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The Infection of Turkeys and Guinea Fowls by the Rous Sarcoma Virus and the Accompanying Variations of the Virus*

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It has been shown (5) that the injection of large amounts of the Rous sarcoma virus into newly hatched ducks was followed by the development of two sorts of tumors, *immediate* and *late*. The immediate tumors occurred from 9 to 30 days after the virus injection, showed much the same features as the original chicken tumor, and could be easily propagated through chickens but not through ducks. The late tumors occurred from 40 to 215 days after injection, showed several new characteristics, and could be easily propagated through ducks but not through chickens. The immediate tumors were the result of a heterologous infection; that is, an infection by a virus that manifests itself at its best in a foreign, heterologous host, whereas the late tumors were the result of a homologous infection by a virus that has changed from its original chicken type to a new duck type. Several duck variants of the Rous virus were thus originated.

When, upon reversing this sequence, chicks were injected with duck tumor viruses, the same phenomena were observed and comparable immediate and late tumors, or other neoplastic lesions, developed from 9 to 100 days and from 45 to 215 days respectively after injection. The following two main characteristic features of the tumors induced in ducks by their homologous viruses are of interest to the subject of the present paper: first, their pronounced collagenous nature, and second, their localization in periosteum and endosteum. These features were also shown in the tumors induced in chickens by the same duck viruses, but were never observed in the tumors induced in the same host by the original Rous virus (4), so that when tumors showing these traits are observed in chickens it is a sign that the virus inducing them has become modified.

In this publication we describe experiments on turkeys and guinea fowls, and also on pigeons and pheasants, analogous to those carried out on ducks, and report results with the two former species essentially duplicating the findings on ducks.

Des Ligneris (3) injected 36 guinea fowls and 24 turkeys with Rous tumor cells in the breast with the result that 21 of the former and 11 of the latter developed tumors. Several of these regressed after an initial growth while others produced metastases in the liver and other viscera, but not in the bones, that led to the death of the animals. The tumors could be passed only to three other series of guinea fowls and 2 of turkeys, all growths eventually regressing, but they grew successfully when grafted back into chickens. Injections of cell-free extracts into turkeys and guinea fowls never induced tumors. "Young and adult" birds were used but their exact ages were not stated.

Andrewes (1, 2) induced tumors in the large majority of adult and young pheasants by injections of both filtrates and cell suspensions of the Rous tumor. Pheasant to pheasant transplantation failed in two series, the tumors regressing after an initial growth or not growing at all. However, in a third series a year later 4 passages of the tumor were effected through younger hosts, and "transplantation could probably have been carried on indefinitely." Regression of the tumors in the course of the passages sometimes occurred. Metastases were present in nearly all tumor-bearing birds, in one case at the site of an old fracture. A hemorrhagic ruptured spleen without grossly recognizable tumor was observed in another case. The tumors in pheasants were usually yellower than in chickens and "sometimes took the form of a thin wall

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of firm, healthy tissue around a hemorrhagic central area." As will be seen later these traits are not unlike those observed in turkeys and guinea fowls and suggest that a variation of the virus might have taken place. Unfortunately, no injections of the pheasant virus into chicks or chickens—the best method of proving such variation—were reported. Cells from 4 other chicken tumors also grew in pheasants.

Fujinami (quoted by Andrewes) reported that his tumor grew in pigeons, quails, and paddy birds, and Oshima (6) succeeded in growing a chicken tumor (Rous?) in 2 species of partridges and in Siamese and green breasted pheasants, while pigeons, sparrows, Java sparrows, canaries, and ducks were found unsusceptible. Some of the tumors, at least, were transplanted back into chickens.

Table I: Effect of Viruses and Cells from Chicken Tumors on Turkeys

Age of birds	1 to 2 days		7 days		21 days		45 to 52 days		60 to 75 days	
Material injected	Number injected	Number with tumors	Number injected	Number with tumors	Number injected	Number with tumors	Number injected	Number with tumors	Number injected	Number with tumors
Rous tumor										
Unfiltered extract	1	1	2	2	2	2	4	3	5	3
Cell suspension	3	3	2	2	2	2	1	1	1	1
Average time of death	11 days		12 days		17 days		17 days		24 days	
Fujinami tumor										
Unfiltered extract	1	1								
Cell suspension	2	2								
Average time of death	10 days									
Chicken tumor B										
Unfiltered extract	3	0								
Cell suspension	8	5								
Average time of death	10 days									

MATERIALS AND METHODS

Most of the experiments to be reported were carried out with the Rous sarcoma while the Fujinami sarcoma and chicken tumor B were tested in a few cases. The latter is a more slowly growing sarcoma than the other two that originated spontaneously and proved to be transmissible by cells or filtrates. All these tumors were maintained by cell passages through full-grown Plymouth Rock chickens.

The guinea fowls and turkeys were hatched for us at the Carman River duck farm, Brookhaven, Long Island, and shipped immediately to our laboratory, where they were inoculated either immediately or kept for several weeks before being used. Adults were generally bought from local dealers. Pigeons, injected shortly after hatching, came from our own colony and were left with their parents until death occurred. Those older than a month were bought from outside local sources. The shortness of the hatching season or difficulties in breeding precluded extensive experimentation on these birds such as was possible with ducklings. Black or white turkeys and guinea fowls and several strains of pigeons were employed. One cubic centimeter of suspensions of tumor cells at a 1:5 dilution and extracts at a 1:9 dilution in saline solution were injected routinely, the former in the breast and the latter in the jugular vein. Berkefeld N candles were employed for filtration. Departures from this technic will be pointed out when the occasion arises. Hematoxylin-eosin and Masson methods were used in the staining of sections.

Turkeys

The results of injecting turkeys from 1 day to 10 weeks of age with unfiltered extracts or cell suspensions of 3 strains of chicken tumors are given in Table I. The extracts were injected into a vein at the ratio of 1 cc. per 30 gm. of body weight; the cell suspensions at 1 cc. for all the birds. The principal conclusions to be drawn from the data are: first, up to 3 weeks of age all turkeys responded to the intravenous injection of Rous tumor extract but this susceptibility decreased in older animals; and second, all turkeys responded to the injection of tumor cells. Viruses and cells from the Rous and Fujinami tumors were more effective than those of chicken tumor B.

Of the 12 turkeys responding to the injection of Rous and Fujinami viruses, splenic tumors were observed in 8 cases, generally in combination with hemorrhagic lesions; periosteal and endosteal tumors in 5 cases, while other organs were involved in 5 cases; tumors in the neck around the injected vein were observed in 4 cases. In the turkeys, 1 day old when injected, the tumors were soft and viscid, much as the original chicken tumors are. These birds developed in addition typical hemorrhagic lesions combined or not with tumors in the viscera and, in the case of Fujinami virus, in the bone marrow. The tumors developing in the spleen or other organs in older tur-

keys were firm, resilient, and a little viscid, and the combination of areas of this tissue with other areas of necrosis gave the tumor a typical pattern approaching that shown by the duck variants of the Rous virus (Fig. 1). Often the spleen was totally replaced by neoplasm. The outstanding microscopic trait of these growths was the production by their cells of large amounts of collagen. These cells showed the pleomorphism usually observed in avian tumors, large, flat, round or oval cells being generally present in the looser areas and large attenuated fibroblasts in the denser areas (Figs. 2 and 3). The periosteal and endosteal tumors were often large, 6×1 cm. in one case, affected several long or flat bones, and resembled, too, similarly induced tumors in ducks (5). Microscopically there was much bone destruction and no formation of new osteoid tissue (Fig. 4).

The growths induced by the injection of cell suspensions from the Rous, Fujinami, and B tumors were again soft and viscid in the turkeys injected at the age of 1 day, but resilient and with the pattern described above in older birds. They varied in size from 3×3 cm. to 7×4 cm., and in 7 of the birds injected with Rous tumor cells metastatic splenic tumors developed that showed the same gross and microscopic traits as the growths induced in this organ by tumor extracts.

Starting from the pooled tumor tissue from 2 turkeys, we carried out passages through other turkeys and also chickens, and this is graphically represented in Fig. 7. Analysis of the results discloses 3 main points:

(a) The tumors were propagated in 4 serial passages through young turkeys by means of cell suspensions or extracts, but the incidence of positive inoculations and of cases with generalization was lower in the last than in the first passages.

(b) No loss of affinity of the virus for its original host, the chicken, occurred as a result of the adaptation of the tumor to the new host, for the turkey tumor was transmitted through chickens in 10 passages. Cell suspensions and filtrates from these chicken tumors were again effective in turkeys in every case where such transmission was attempted.

(c) The virus of the Rous sarcoma of chickens varied on adaptation of the tumor to turkeys as attested by the following facts: First, the turkey virus injected back into an adult chicken at the third passage induced a widespread neoplastic disease involving bones—periosteal and endosteal tumors—and the same lesions developed in 2 more chickens of the line started from these tumors. Second, 4 of 6 adult chickens responding to inoculation at the fifth and sixth passage developed pronounced hemorrhagic lesions, which in adult chickens injected with the original Rous virus occur only exceptionally in birds with a low content

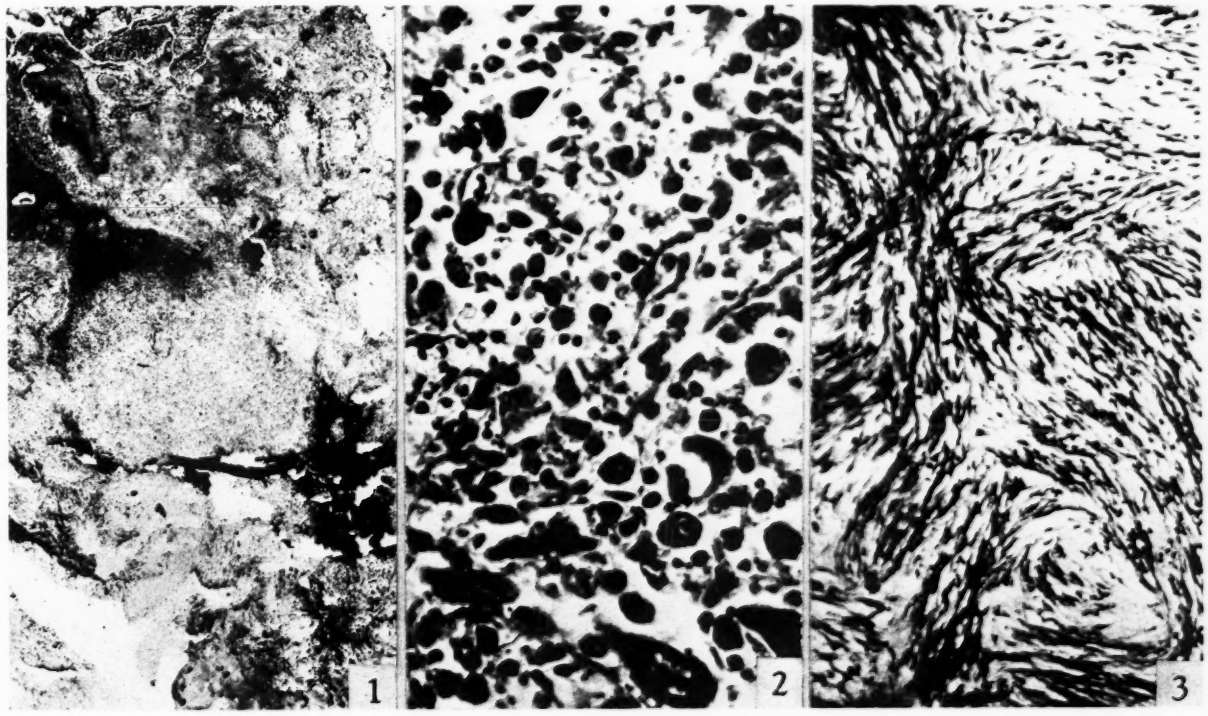

FIG. 1.—Tumor in spleen of a turkey injected intravenously at the age of 9 weeks with 4 cc. of 1:10 extract of Rous sarcoma. The bird was killed 34 days later and the spleen tumor measured 5 × 3 cm. Mag. × 9.

FIGS. 2 and 3.—Two fields of the same tumor showing cell pleomorphism. Tissue of Fig. 3 stained deep green with Masson method. Mag. × 550.

in natural specific antibodies and dying soon of their rapidly growing tumors (4). Yet 2 of our chickens died after 25 days, only as a result of hemorrhage, and the other 2 lived as long as 53 and 90 days.

The tumors in the course of the passages through turkeys showed the same gross and microscopic traits as those directly induced in these hosts by the Rous virus and, characteristically, spleen and bones were frequently involved. Two of the turkeys injected intravenously with filtrates, one at the age of 3 days (2nd passage) and the other at the age of 40 days (4th passage), showed tumors in practically every bone combined with hemorrhagic lesions. In the other turkeys breast bone and ribs were involved by preference. Tumors in other tissues were observed only occasionally.

Tumors induced in chickens by materials from turkey growths showed much the same pattern and texture and secreted collagen as did the turkey tumors, still another proof of virus variation to be added to those above recorded. The bone tumors were small, and involved the ribs in 2 cases and the wing bones in the third case (Fig. 5). The hemorrhagic lesions were located in the liver, where collections of blood sometimes 5 cm. in diameter were observed, and to a lesser extent in the spleen. All these characteristics of chicken tumors seemed to wane in the course of transplants and in the last 5 passages the tumors were soft and showed much viscidity. Bone involvement was never observed and hemorrhagic lesions were observed only once. Possibly the virus was reverting to the original Rous type.

Four passages through young turkeys were carried out also from pooled neoplastic and hemorrhagic lesions from a turkey injected intravenously with an extract of Fujinami tumor, with results comparable to those obtained with the Rous virus, but no bone involvement was observed. On the contrary, passages attempted from 4 different tumors induced in turkeys by cell suspensions of chicken tumor B resulted in failure.

FIG. 4.—Sarcoma of endosteal origin in a bone of a turkey from the second passage. The bird was injected intravenously with tumor filtrate at the age of 2 days, and died 13 days later with generalized neoplastic and hemorrhagic disease involving most long bones. Mag. × 125.

FIG. 5.—Sarcoma in wing bone of a chicken injected intramuscularly with virus of the third turkey passage, and dying 22 days later.

FIG. 6.—Sarcoma in leg bone of a guinea fowl injected intravenously at the age of 2 weeks with Rous tumor extract. The bird died 59 days later with tumors in spleen, lung, and bones. Note pronounced formation of osteoid tissue. Mag. × 12.

Guinea Fowls

The response of guinea fowls of varying ages to filtrates and cell suspensions of the Rous sarcoma was next investigated (Table II). It is evident that the age susceptibility of these birds is more restricted than that of turkeys, since guinea fowls only 5 weeks old were found already refractory.[1]

as 3.0 × 3.0 cm. in one instance, surrounded by clotted blood in 2 birds while in the fourth bird it was wholly replaced by a clot. This duplicates comparable findings on pheasants by Andrewes (2) and by us on chicks (4). The tumors in both young and older birds were firm, resilient, not viscid, showed large areas of necrosis, and had a general pattern very much

Table II: Effect of Virus and Cells from Rous Sarcoma on Guinea Fowls

Age of birds	1 to 2 days		14 days		38 days		210 days	
Material injected	Number injected	Number with tumors	Number injected	Number with tumors	Number injected	Number with tumors	Number injected	Number with tumors
Filtered extract	3	2	2	2	2	0	2	0
Average time of death	50 days (killed)		60 days					
Cell suspension	7	7	2	1	2	0	2	0
Average time of death	17 days		120 days					

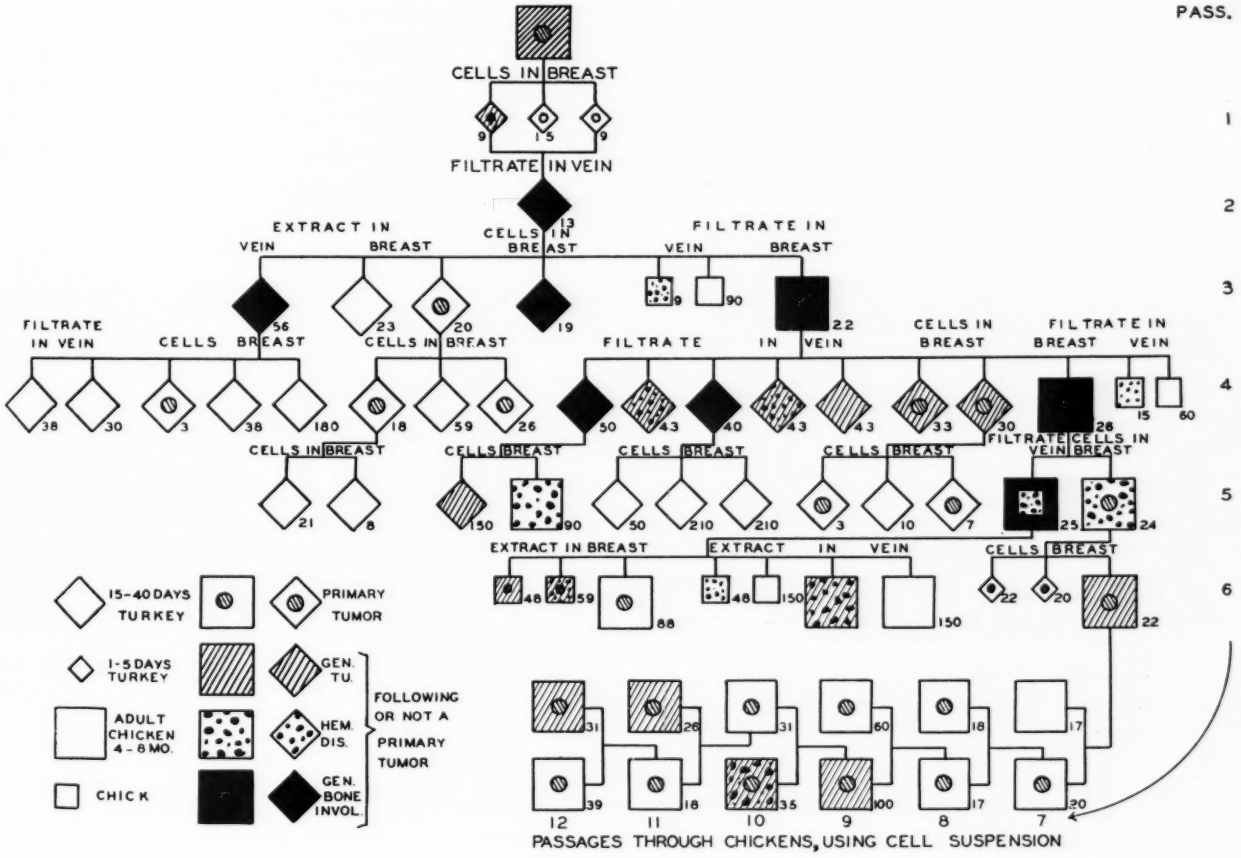

Fig. 7.—Transmission of Rous tumor to turkeys. Conventional signs as expressed above representing two different sorts of lesions are sometimes combined. The small figure underneath the sign indicates the number of days subsequent to injection at which the animal died or was killed. Gen. tu. = Generalized tumors. Hem. dis. = Hemorrhagic disease. Gen. bone invol. = Generalized lesions with bone involvement.

The virus injected intravenously constantly affected the spleen. The organ was a mass of tumor, as large like that of turkey tumors. Microscopically, the same combination of large, round, flat cells and long attenuated fibroblasts was observed, and again the most distinctive trait was the great amount of collagen secreted. Endosteal tumors occurred in 2 cases. There was a massive involvement of the marrow cavity and a notable production of osteoid tissue (Fig. 6).

[1] However, one guinea fowl injected intravenously with Rous virus at the age of 5 weeks died 32 days later of a condition involving practically all bones and characterized by pronounced fibrosis and the formation of new osteoid tissue analogous to what is found in osteopetrosis of chickens (5).

The growths induced by the inoculation of cell suspensions measured from 1.0×1.0 cm. to 5.0×3.0 cm. and produced metastases in 3 cases in the spleen and liver, while hemorrhagic lesions were observed in the lung and bone marrow besides the organs showing neoplasia. Histologically the tumors were like those induced by filtrates.

Passage of 4 of the tumors to other guinea fowls was attempted with success in one case (Fig. 8). From

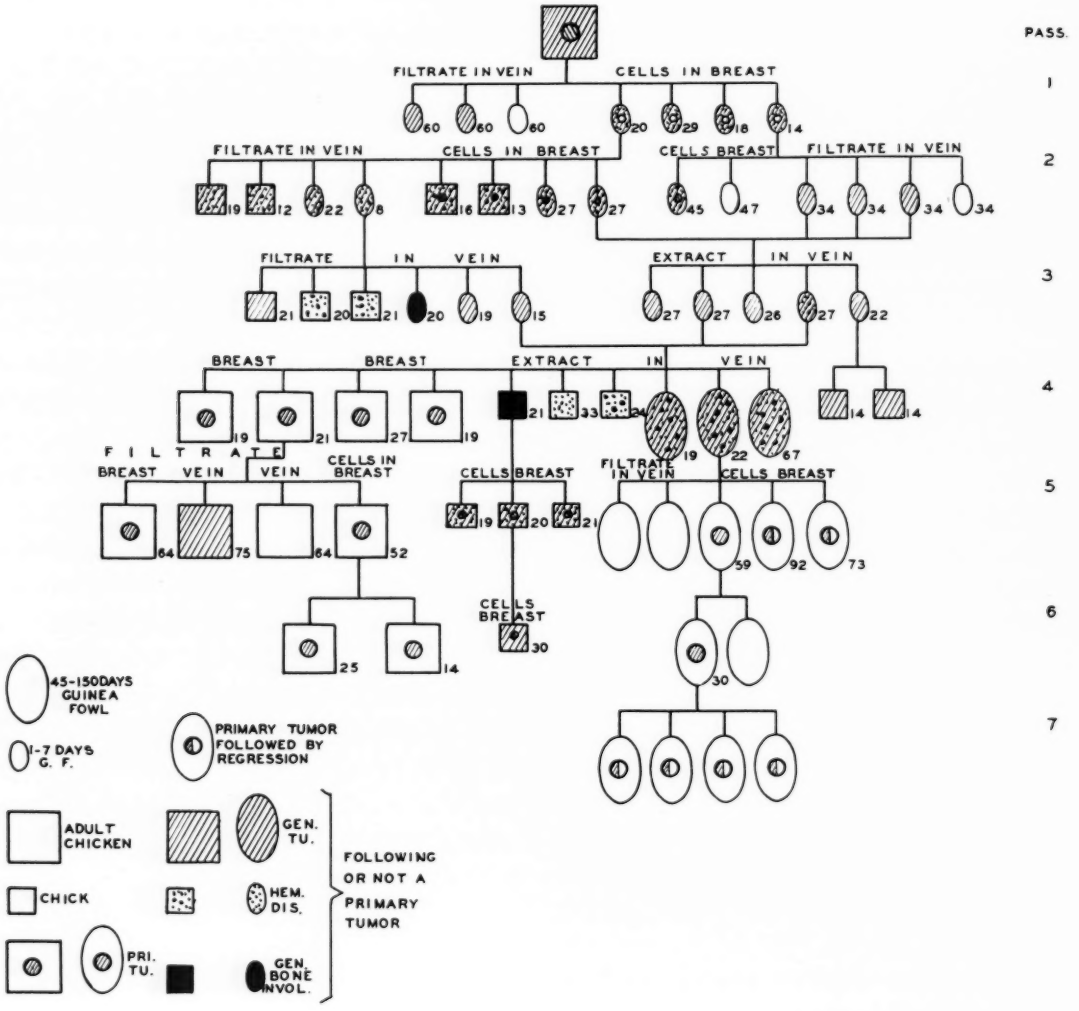

FIG. 8.—Transmission of Rous tumor to guinea fowls. See Fig. 7 for legend.

the data the following main points emerge, almost a duplication of those observed in turkeys:

(a) A line of guinea fowl tumors was established that grew successfully in young birds in 4 passages but less so in older birds, since regression occurred frequently, in 2 more passages.

(b) The adaptation of the tumor to guinea fowls did not result in any loss of affinity for chickens.

(c) A variation of the chicken virus occurred, as shown by the following facts: First, the passage tumors grew progressively or temporarily in birds from 6 weeks to 4 months of age that would have been wholly refractory to the original chicken tumors. Second, periosteal and endosteal tumors were occasionally induced in chicks (Fig. 9) injected with the guinea fowl tumor virus.

The distribution of the tumors in guinea fowls in the course of the passages differed somewhat from that in turkeys. Periosteal and endosteal tumors were observed only once, but the spleen and liver were almost constantly studded with metastases (Figs. 10 and 11). These lesions developed either as a direct effect of the virus injected intravenously or as metastases of primary breast tumors. Both primary and metastatic tumors showed the same pattern and microscopic features as the tumors induced in guinea fowls by the chicken virus. Hemorrhagic lesions were present as a rule in young birds either in association with the tumors or independent of them in the bone marrow and lungs. All these features were retained to a large extent in the lesions transmitted to chicks

and chickens by means of filtrates or cell suspensions, and in the following generations of the resultant tumors through other chickens. Characteristically, the primary breast tumors showed large cavities, generally full of blood, into which protruded tumor nodules arising from their walls, much the same as Andrewes

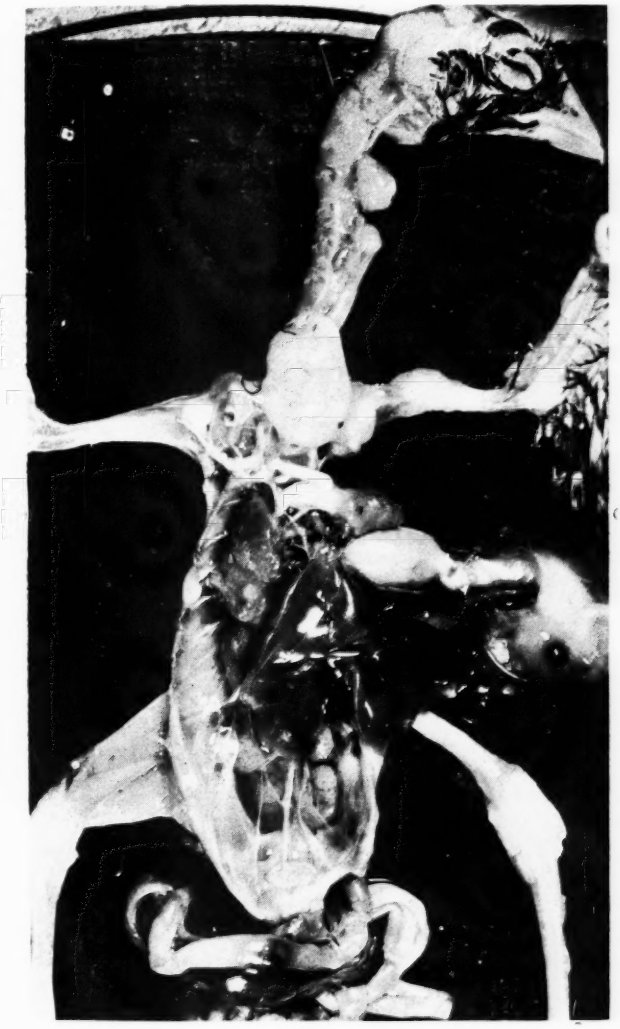

FIG. 9.—Periosteal sarcomas in skull and humerus and ordinary sarcomas in soft tissues of neck, in a chick injected intravenously at the age of 2 days with virus from guinea fowl tumor of the fourth passage and dying 21 days later. Another periosteal sarcoma developing in the right tibia is only partly seen. Note typical hemorrhagic bleb in the gizzard. Reduced ⅓.

described in pheasant growths (1). Hemorrhages into the lung and bone marrow were common occurrences in chicks.

PIGEONS

Pigeons 2 hours old were injected intravenously with 0.1 cc. of filtrate of Rous sarcoma at 1:10; those 1 to 3 days old with 0.5 cc., and the dose was progressively increased up to 2 cc. in the other pigeons according to their age. In the older birds unfiltered extracts and also 1 or 2 cc. of cell suspensions were injected into the breast and the former also into the jugular vein. The results, summarized in Table III,

FIG. 10.—Usual appearance of the liver in guinea fowls injected with filtrate or cells of the passage tumor. Reduced ⅓.

plainly show the complete resistance of pigeons of all ages to both tumor virus and cells. On three different occasions tissues from the injected birds were extracted and injected into other pigeons with negative results.

PHEASANTS

These tests were carried out 6 years ago on full-grown birds with the purpose of confirming Andrewes' results. A pair were injected in the breast with 2 cc. of cell suspension of Rous tumor. Tumors developed

in a few weeks that were successfully passed to another pair of birds. No chicks or chickens were injected with pheasant virus.

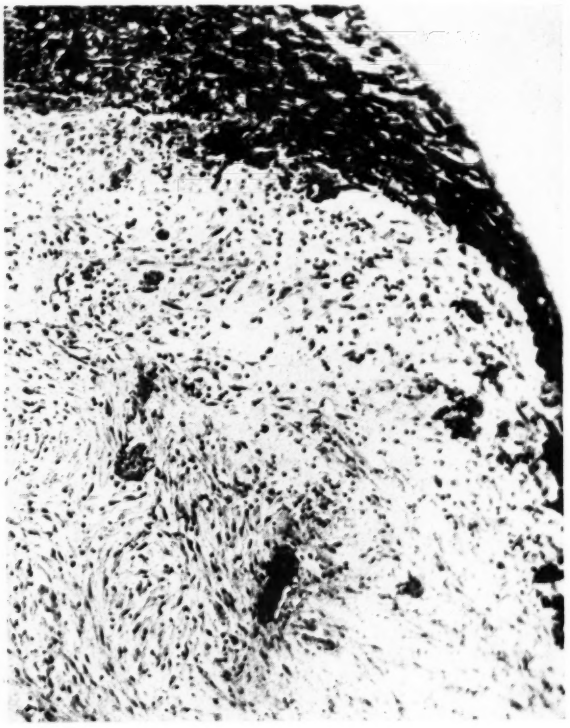

FIG. 11.—Microscopic view of one of the liver tumors of Fig. 10. Mag. × 150.

One can say, therefore, that with the possible exception of growths in 1 day old turkeys no immediate tumors, that is, tumors induced by the heterologous unchanged chicken virus, were obtained, the virus evidently varying and the tumors adapting themselves to the new host at once. These tumors presented new and characteristic features, although not so distinctive as those of comparable duck tumors, and these features were shown also by the tumors produced by cells of the Rous sarcoma, so it is questionable whether multiplication of the injected cells played an important part in these growths.

In ducks the acquisition by the virus of new host affinities was accompanied by a complete loss of its original affinities for chickens. Not so in turkeys and guinea fowls; but the tumors induced in chickens by the tumor viruses from these two species had the same characteristics and distribution as those induced in turkeys and guinea fowls themselves. This was the clearest proof that the virus had varied.

In ducks the new lines of tumors were stable from the first passages whereas this did not seem to be the case with the turkey and guinea fowl lines. Conceivably, though, if a larger number of birds had been injected stable lines might also have been obtained through further adaptations of the tumors.

Therefore it would seem that there is an inverse relation between the degree of the virus variations as manifested by the loss of original species affinities, stability of the new tumor lines, characteristics of the growths, etc., and the frequency with which these variations take place. In other words, the higher its frequency the less pronounced is the variation. This frequency is conditioned by some inherent factor of the species in which infection is attempted, probably its place in the zoological scale in relation to chickens, and by the age of the individual injected. The species studied range in susceptibility to the Rous virus as follows: pheasants, turkeys, guinea fowls, and ducks. It is known that it is possible to obtain chicken-pheasant hybrids. Pigeons from 1 hour to several weeks of age were found wholly unsusceptible within our experimental conditions.

It is worth noticing that the ability of the chicken tumor virus after variation to localize in the periosteum

TABLE III: EFFECT OF VIRUS AND CELLS FROM ROUS SARCOMA ON PIGEONS

Age of birds	2 hours		1–2 days		8 days		30–50 days	
Material injected	Number injected	Number with tumors	Number injected	Number with tumors	Number injected	Number with tumors	Number injected	Number with tumors
Filtered or unfiltered extracts	1	0	6	0			8	0
Cell suspension			1	0	2	0	2	0
Average time of death	12 days		22 days (some killed)		240 days (all killed)		75 days (all killed)	

DISCUSSION

The findings in turkeys and guinea fowls are to be compared with those in ducks similarly infected with the Rous sarcoma virus (5). Ducks were found to be susceptible for only 1 day after hatching; only 22 per cent of them developed tumors, and in only a fifth of these tumors did the virus vary and become adapted to the new host, this last taking place generally several months after infection. In contrast with this, 80 per cent of the guinea fowls injected with Rous virus were found susceptible for at least 2 weeks; 78 per cent of the turkeys for at least 10 weeks; and in practically all cases the virus acquired new tissue affinities, besides the new host affinities, became capable of infecting older hosts that would be refractory to the original chicken virus, and killed them in a few weeks.

or endosteum and to induce collagenous growths is a characteristic common to several duck and to all turkey and guinea fowl variants obtained.

Finally, if one still doubted that the late tumors induced in ducks by the Rous sarcoma virus are not variants of the virus but are induced by hypothetical tumor viruses latent in the duck tissues, such doubts should be dissipated by the present findings. For it would be absurd indeed to deny that such a high proportion of analogous tumors developing in turkeys and guinea fowls only a few weeks after the injection of the chicken virus is due to something other than that virus.

SUMMARY

About 80 per cent of turkeys within the first 10 weeks after hatching were found to respond to intravenous injections of Rous sarcoma virus and the same was true for guinea fowls within the first 5 weeks of life. When cell suspensions were injected the incidence of tumors rose to 100 and 88 per cent respectively. A few adult pheasants injected with cells proved also to be highly susceptible, while newly hatched or older pigeons were found wholly refractory to both virus and cells.

The tumors induced were maintained through 4 passages in turkeys and 6 in guinea fowls by inoculation of tumor extracts or cell suspensions, but the growths were less vigorous, especially when older animals were injected. Both original and transplanted tumors in guinea fowls and in most turkeys were but slightly viscid, very collagenous, and had a pattern approaching that shown by the duck variants of the Rous virus.

The tissue affinities of the viruses were also characteristic. Frequently in turkeys and occasionally in guinea fowls periosteal and endosteal tumors developed, and in the latter hosts the spleen and liver were always typically and almost exclusively involved.

The species affinities of the virus were not modified by the adaptation of the tumors to the new species as was the case in ducks. The viruses of the turkey and guinea fowl tumors regularly infected adult chickens but they showed in these hosts the same tissue affinities, periosteum and endosteum, and induced collagenous tumors much as in their respective homologous hosts. The disease in chickens showed other features in addition whereby it could be differentiated from that induced in them by the original Rous virus.

It is concluded that the virus of the Rous sarcoma of chickens has undergone variations in turkeys and guinea fowls and the characteristics of these variants are discussed, especially in their relation to the duck variants previously obtained.

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Growth of a Chicken Sarcoma Virus in the Chick Embryo in the Absence of Neoplasia*

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Previous studies from this laboratory (2) showed that chickens injected intravenously with the viruses of the Rous and Fujinami sarcomas responded with notably different types of lesions according to the age of the bird. In the newly hatched chick, a host devoid of virus-suppressing antibody (3), the disease frequently revealed itself by the exclusive development of hemorrhagic lesions in the absence of grossly detectable neoplasia. In pullets neoplasia was observed side by side with hemorrhage. In the adult chicken, a host endowed with virus-suppressing antibody, the lesions when present were mostly neoplastic. The naturally developing virus-suppressing antibody not only conditions the age resistance but also the individual resistance of chickens to tumors (3). Its importance in conditioning the virus activity was further shown (4) by the fact that in chicks infected intravenously with the Rous virus and treated daily with serum from normal adult chickens there was a shifting from hemorrhagic to neoplastic lesions or a complete absence of all lesions.

Histologic study of the early hemorrhagic lesions in chicks failed to disclose neoplasia, and after discussion of the different mechanisms that may lead to hemorrhage the possibility was considered that this hemorrhage may result from direct action of the virus on the vessel wall; however, proofs of a necrotizing effect on its endothelial cells or fibroblasts were lacking. It was then decided to extend the studies to chick embryos, a still more vulnerable host than the newly hatched chick, with the hope, first, that serial sections of the whole embryo would bring irrefutable proof concerning the lack of neoplasia, and second, that the destructive vascular lesions that may lead to hemorrhage would be shown in these hosts. The present paper records the results of inoculating filtered or unfiltered extracts of the Rous sarcoma into the celomic cavity and blood stream of 3 day old chick embryos and outlines a few similar experiments in older embryos.

Murphy and Rous (9) transplanted Rous tumor cells into many chick embryos at the seventh or eighth day of development with the result that tumors in the membranes developed in most instances. By indiscriminate implantation growths were also induced in the embryo along the track of the needle. Of 23 embryos grafted at the second or third day of development in the outer zone of the blastoderm only 5 showed small growths. Tumor filtrates and suspensions of desiccates injected into embryos presumably 7 or 8 days old induced tumors noticeable 3 or 4 days later and having the same location as those produced by living cells. No blood-born metastases occurred. No mention is made of hemorrhagic lesions in the embryo or membranes although it is stated that hemorrhage in the tumor substance was not uncommon.

Other observations on the hemorrhagic lesions occurring in tumor-bearing chickens have been reviewed in a previous publication (2).

MATERIALS AND METHODS

The host animal used routinely in these experiments was the 72 hour white Leghorn chick embryo. Instances in which other stages of development were made use of are indicated in the results. Rous sarcoma extract, 1:5 and 1:10 in normal saline, and Rous filtrate 1:10 (Berkefeld N) were injected in quantities up to 0.05 cc. In operating, a rectangular window was cut in the shell and its membrane and the embryos thus exposed. A manually controlled glass micropipette was then introduced either into a vein or into the celomic cavity, and the inoculum injected under pressure. All injections were intracelomic unless otherwise indicated in the text. The shell was then replaced, and the embryos incubated either until candling indicated death or until an adequate period of development had elapsed.

Tissues sectioned were fixed in formol, cut at 10 microns, and stained in hematoxylin and eosin. The presence of virus in the diseased embryos was investigated by injection of their extracts at 1:10 in saline solution into a pair of normal barred Rock chicks or pullets. Bacteriological examinations were routinely made.

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Intracelomic Injections of Filtered Tumor Extract

Experiment 1.—A preliminary series of ten 72 hour embryos was injected with 0.05 cc. of 1:10 tumor filtrate and examined after 8 days' incubation. One was found to have hemorrhagic blebs in the heart, lung, and liver, and another to have identical lesions in the heart, lung, and proventriculum. The viscera of these embryos were pooled and extracted, and those from two that showed no lesions were similarly extracted. Of these respective extracts 1 cc. was injected subcutaneously into right and left breast areas of pullets. In each case the extracts of embryos with demonstrable lesions induced tumors, while those from embryos with no visible lesions did not.

Experiment 2.—Inoculum, 0.05 cc. tumor filtrate; 16 recipients.

7 days after injection.—Of 5 embryos examined, 1 had a hemorrhagic bleb on the right ventricle.

8 days after injection.—Three of 11 embryos opened showed lesions. Each of these had subepicardial petechiae, and one had blebs within the breast musculature. These lesions, with the immediately surrounding tissues, were extracted and the extract was inoculated into a series of 72 hour embryos, which failed to develop lesions. The remaining viscera of embryos with lesions, and those from embryos that were normal in appearance, were extracted by identical methods and the extract was injected into the breasts of pullets. Again, extracts from embryos with lesions induced tumors, while those from healthy embryos did not.

Experiment 3.—Inoculum, 0.05 cc. tumor filtrate; 14 recipients.

14 days after injection.—Dissection of one dead embryo revealed a single hemorrhagic lesion on the liver. An extract of this embryo was injected into the celomic cavities of 14 chick embryos 3 days old with the result that one embryo, which hatched and died on the 21st day of incubation, developed blebs on the liver and spleen and its extracts induced tumors in pullets; the other embryos of this group died without lesions and their extracts did not induce tumors in pullets.

17 days after injection.—Of 6 embryos opened, one had on the chorioallantoic membrane a small white, soft, nodular tumor that measured 1.5 mm. in diameter. The embryo itself had hemorrhagic blebs on the spleen and heart. The tumor was extracted and the extract injected into seven 3 day chick embryos and two chicks; one embryo developed a typical bleb on the liver after 11 days, and the chicks died of tumors after 1 month. Extracts of the viscera of the tumor-bearing embryo induced neoplasia when injected into pullets. Other embryos of the series died without lesions.

Experiment 4.—Inoculum, 0.5 cc. 1:10 tumor filtrate; recipients, six 6 day embryos.

4 days after injection.—Dissection of 4 embryos revealed no lesions.

17 days after injection.—Two embryos hatched and examination showed small heart blebs. Their viscera were extracted separately, and the respective extracts induced tumors in chicks in one instance, not in the other.

Experiment 5.—Inoculum, 0.5 cc. 1:5 tumor filtrate; recipients, seven 13 day embryos; intravenous inoculation.

6 days after injection.—Two embryos examined showed no lesions.

7 days after injection.—Four embryos opened were found to have subepicardial petechiae, but no other lesions. However, extracts of these embryos induced tumors when injected into chicks.

18 days after injection.—Two animals hatched, of which one had developed myocardial blebs.

In an additional series 1 cc. of 1:5 Rous filtrate introduced upon the chorioallantoic membranes of 13 day embryos elicited no response whatsoever.

Experiment 6.—Small fractions of a cubic centimeter of 1:10 Rous filtrate were injected intravenously into six 3 day chick embryos. After 10 days one embryo had widespread subcutaneous petechiae but no definite blebs. However, extracts of this embryo were effective in inducing tumors in chicks.

Intracelomic Injections of Unfiltered Tumor Extract

Experiment 7.—Inoculum, 0.05 cc. unfiltered tumor extract; 13 recipients.

5 days after injection.—Five embryos dissected, of which 2 had developed hemorrhagic lesions.

Over the next 4 days 8 embryos died and were dissected. Each of them had extensive hemorrhagic disease.

Experiment 8.—In this experiment serial passages of the hemorrhagic disease through 6 groups of 3 day old embryos were accomplished. The embryos of the first passage were injected intracelomically with 0.05 cc. of unfiltered tumor extract 1:10. Subsequent passages were carried out by injection of the same amount of embryo extract 1:5 and proved to be sterile by cultures. The results are summarized in Table I.

Experiment 9.—Inasmuch as the time interval between injection and the development of lesions in the passage series described above was moderately uniform in the second, third, and fourth passages, and since the majority of embryos examined at the time specified were dead, we decided to run a second series, opening the recipient embryos 7 days after injection, thus using live embryos with lesions for the preparation of ex-

tracts. The embryos selected in each case had widespread hemorrhagic lesions, and 1:5 extracts were employed in each instance. The results, given in Table II, showed again that the hemorrhagic disease could be serially transmitted through embryos.

Summarizing the outcome of the entire series of experiments one can state that about 40 per cent of the

TABLE I: FIRST SERIAL PASSAGE OF THE ROUS VIRUS THROUGH 3 DAY OLD CHICK EMBRYOS

Passage No.	Number of embryos	Time after injection when embryos died or were killed, days	Number showing hemorrhagic lesions	Results of injecting embryo extract into pullets
1	12	14	1	
2	7	7	5	Tumors
3	12	8	10	Tumors
4	18	9	3	Tumors
5	12	25	1	
			(after hatching)	

Passage to the fifth series of embryos was made by the injection of extract of a desiccate prepared from the embryos of the fifth passage. The process of desiccation reduced either the virulence or the relative amount of the virus, because among 12 embryos lesions were observed in the heart and liver of the only individual that hatched and was killed 7 days later.

TABLE II: SECOND SERIAL PASSAGE OF THE ROUS VIRUS THROUGH 3 DAY OLD CHICK EMBRYOS

Passage No.	Number of embryos	Time after injection when embryos were killed, days	Number with hemorrhagic lesions selected for next passage	Results of injecting embryo extracts into chicks
1	12	7	2	
2	16	7	2	Tumors
3	8	7	4	Tumors
4	5	7	2	Tumors
5	6	7	2	
6 *	5	7	2	
7 †	6	7	0	

* The embryos were extracted after having been kept frozen for 4 days. Again the preservation of material for subsequent injection resulted in loss of potency of the inoculum.

† Some of the embryos of this series were allowed to continue development until the 11th postinjection day. Upon dissection at this time, one animal was found to have a small nodular tumor on the chorioallantoic membrane. This tumor was excised from the living animal and transplanted to the celomic cavities of two 72 hour chick embryos. The tumor tissue grew but the embryos, dissected 5 and 9 days after implantation, had developed hemorrhagic blebs without evidence of tumor extension or metastasis.

119 embryos 3 days old when injected with the virus intracelomically developed hemorrhagic lesions. Embryos 6 and 13 days old, 13 in number, responded to intracelomic or intravenous inoculation in 60 per cent of cases, but the amount of virus injected was larger and the disease apparently less severe, 3 of the injected embryos hatching and living for a few days. In experiment 7 possibly all the thirteen 3 day old embryos thus injected would have died of their hemorrhagic lesions. It is clear, however, that the above figures are far from representing exact percentages of susceptibility since many embryos were purposely killed at an early date and others died of incidental causes.

The tumors induced in chicks and pullets by extracts of diseased embryos did not differ in any way from the tumors induced in these hosts by the ordinary tumor virus or cells.

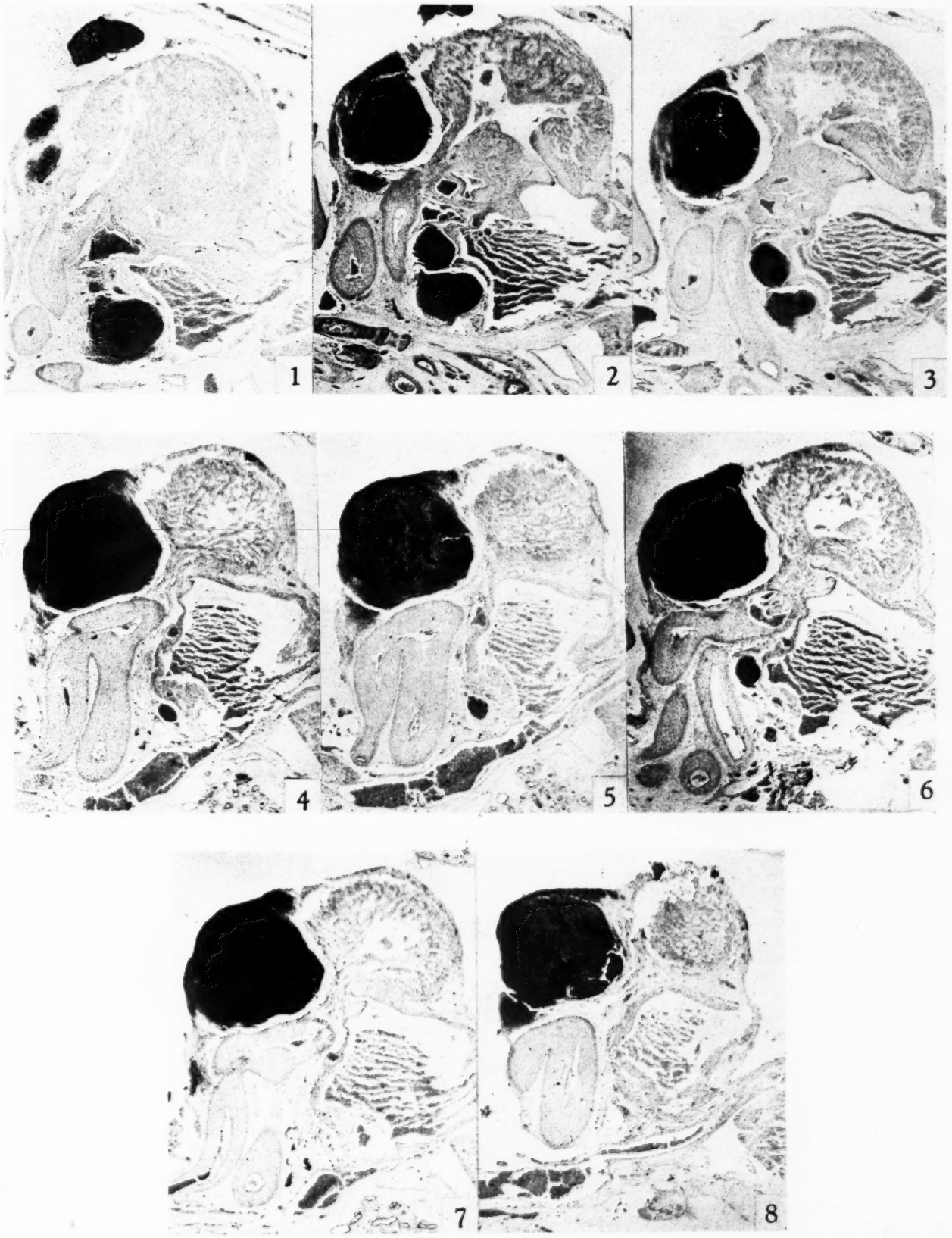
The most important observation made during the experiments was the complete absence of grossly detectable neoplasia in the embryos. In 2 cases tumors developed but the growths were incorporated within the tissues of the chorioallantoic membrane and had not penetrated the embryo proper either by extension or by metastasis, although in one case the embryo itself showed hemorrhagic lesions.

Histological studies.—The nonneoplastic nature of the hemorrhagic lesions of the embryos was fully corroborated by microscopic examination of sections from many lesions and of sections mounted in series at 100 micron intervals of entire embryos (Figs. 1 to 8).

Findings suggesting direct or indirect destructive effects of the virus were largely confined to hemorrhages into the subepicardial tissues, liver (Fig. 9), and spleen (Fig. 10), and to the considerable edema, which was largely limited to the cutis but which was present also in the myocardium and great vessels leaving the heart. Some cell necrosis was present in these areas, but no infiltration. Desquamation and slight swelling of the endothelium was noticed in the hemorrhagic areas, but no undue mitosis. Capillaries were frequently surrounded by blood elements, but in no instance were these of such a type as to suggest that anything more than rupture of capillary walls had preceded their aggregation in these sites. The tumors that in two instances developed in the chorioallantois were loose sarcomas of the ordinary type.

Control injections.—Often during the course of the passages extracts from normal chicken embryos were injected intracelomically into 3 day embryos without lesions resulting in any case.

Attempts to protect the embryo against the virus by means of serum from normal adult chickens.—Several experiments of this sort were carried out in an attempt to duplicate on embryos what had been achieved in chicks (4). In one experiment, adult serum incubated with an equal quantity of tumor extract during 1 hour failed to prevent the appearance of hemorrhagic lesions in nine 3 day embryos. There was, similarly, no protection provided to twelve 3 day old embryos that received adult serum 2 days subsequent to the tumor extract, or to another twelve that received the extract 12 days subsequent to the adult serum. It will be remembered that in chicks, too, protection was



FIGS. 1 to 8.—Serial sections showing the heart and adjacent regions of one of the embryos of experiment 9. The deeply staining area is subepicardial hemorrhage. Because no definitive lesion other than hemorrhage and edema could be made out, higher magnifications were not photographed. Mag. × 12.

achieved only when the serum was injected during several successive days, a single high dose being ineffective. Daily successive injections were tried in embryos also but this resulted only in their premature death.

but no lesions occurred. Another 5 embryos received small implants of Rous tumor in the chorioallantois. Two hatched, and these died 3 and 5 days later with hemorrhagic and neoplastic lesions in the heart, lungs, spleen, and liver.

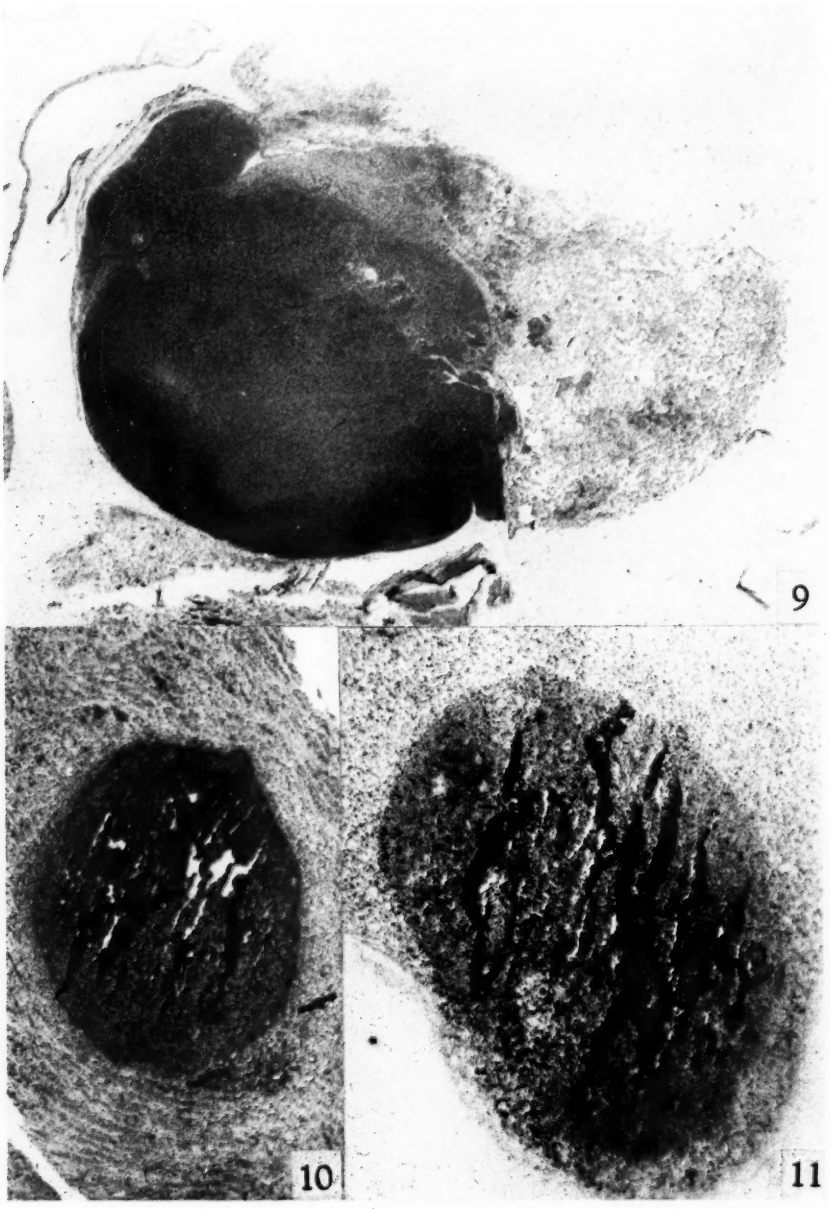


FIG. 9.—Section through an excised liver bleb. The almost indiscernible border between liver tissue and hemorrhage is typical. Mag. × 95.

FIG. 10.—Section through a bleb in the spleen of an embryo. The tissues surrounding appear normal. Mag. × 95.

FIG. 11.—Bleb in breast muscle of an embryo. Hemorrhages occurred not infrequently in skeletal muscle and in subcutaneous connective tissue. Mag. × 40.

Experiments on duck embryos.—Murphy and Rous (9) grew the chicken tumor in duck embryos, but did not mention the occurrence of hemorrhagic lesions. We injected intravenously 60 duck embryos at the 18th day of incubation with 0.5 cc. of tumor extract

DISCUSSION

Since microscopically and in the gross no neoplasia was observed in the numerous lesions studied and in whole embryos serially sectioned it would seem that the only reason for persistence in maintaining that

hemorrhage is the result of tumor growth would be the reluctance to admit that a cancer virus can behave as an ordinary cell-destroying virus under certain conditions.

Yet this conclusion is upheld by the fact that destructive lesions in the capillary endothelium and underlying connective tissue were observed. Although of a much milder sort, they can compare with similar lesions induced in the chick embryo by necrotizing viruses, *e. g.*, herpes virus, as shown by Anderson, and hemorrhage was induced by that virus also (1). It is easily conceivable that the weakened vessel wall gives way under the blood pressure and "blebs" form that may or may not rupture. Let us point out here that in young birds these typical lesions have been observed with all viruses studied that induce sarcoma in chickens, ducks, turkeys, and guinea fowls (2, 5, 7).

It is quite conceivable also that the destructive lesions are more clearly shown by the early embryo than by chicks injected at the age of 1 day, and dying several days later, because the processes of immunological maturation are detectable very early after hatching.[1] Anderson (1) observed, too, a pronounced resistance to herpes virus in the 18 day chick embryo as compared to the 9 day embryo, and it is important to note that the resistance of the older embryos manifested itself by the development of proliferative lesions in the membranes, whereas the susceptibility of the younger embryos was shown by necrotizing lesions.

Still other reasons for the lack of hemorrhagic lesions in more resistant chickens showing widespread neoplastic involvement of tissues and vessels have been considered in another discussion (2).

There is an apparent contradiction between our results and those of Murphy and Rous (9), who induced tumors in the membranes of embryos and in the embryos themselves with tumor filtrates or desiccates at 7 to 8 days' incubation and reported no hemorrhagic lesions. While the embryos used routinely in the present investigation were 4 or 5 days younger one must point out that 6 and 13 day embryos (experiments 4 and 5) injected intravenously with tumor filtrate and allowed to develop for 7 days showed mild hemorrhagic lesions, but no tumors. Neoplasia in the chorioallantois developed in only 2 cases, and in one of them typical hemorrhagic lesions developed in the embryo but no tumors. The same occurred in another case when tumor tissue was implanted in the membrane.

An important point to keep in mind in trying to explain these discrepancies is that besides injecting older embryos Murphy and Rous worked with a virus from the earliest passages, therefore with one far less active than ours.[2] Hence, the discrepancy seems to indicate that the same "tumor" virus in a state of low activity for adults induces neoplastic lesions in most cases in the highly susceptible embryo, whereas in a state of high activity for adults it induces destructive lesions, followed or not by hemorrhage, in embryos and young birds. That the virus inducing neoplasia or cell destruction is the same is shown by the fact that in the present investigation the injection of the embryo lesions into older hosts consistently resulted in tumors.

The principle outlined above is essentially the same as that previously enunciated (3, 4), and further confirmed in this study; namely, that neoplasia by chicken "tumor" viruses of high activity evolves only when the host is endowed with a certain resistance against these viruses. A higher resistance results in no lesions; a lower resistance in destructive ones.

Other data supporting these views have been brought forward in relation to the virus of rabbit fibroma (6) and will be reported in future publications.

SUMMARY

The virus of the Rous sarcoma of chickens injected intracelomically or intravenously into a total of 132 three, six, and thirteen day chick embryos multiplied in 64 of these hosts without eliciting tumors, but produced hemorrhagic lesions in all 64 analogous to those previously described in chicks.

These lesions were serially transmitted to other embryos in 6 successive passages, again without induction of neoplasia.

The injection of extracts of these lesions, however mild, into chicks and pullets resulted in tumors of the ordinary type, but embryos in which no lesions developed apparently contained no transmissible virus.

Tumors in the chorioallantois developed in only 2 of the 64 embryos that developed lesions. Thus such growths may coexist with typical hemorrhagic alterations in the embryo proper.

Microscopic study of the hemorrhagic lesions disclosed the presence of destructive changes in the vessel wall and adjacent connective tissue and confirmed the absence of neoplasia.

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[1] The blood serum from 24 hour old chicks occasionally contains enough natural viral antibody for the Rous virus to be demonstrable by available neutralization tests. Serum from 5 hour old ducklings already contains natural neutralizing antibodies for the virus of the duck variant of the Rous sarcoma (8).

[2] At the time Murphy and Rous carried out their investigation the tumor was still in a phase before the sixth passage, when it succeeded only in Plymouth Rock chickens. Maximum malignancy was attained at the sixth passage and hemorrhagic lesions in highly susceptible chickens were not observed until the eighth passage, 15 months from the time of the original transplantation (10).

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Studies on Rous Sarcoma Cells Cultivated in Vitro*

II. Morphologic Properties of Rous Sarcoma Cells

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In the preceding paper of this series we described the cellular composition of pure cultures of the Rous sarcoma and the relationships between the cell types of which it is formed. We showed that such cultures consist of two types of cell, basophilic round cells and spindle cells, that are closely related and may turn one into the other.

In our previous investigations the morphological analysis was confined exclusively to a description of these two varieties in their basic forms. The study of pure strains *in vitro* shows, however, that in the course of cultivation cells bearing the Rous agent undergo important alterations, which decidedly change their aspect. To the description of these variations the present paper is devoted.

MATERIAL AND TECHNIC

The material and technic employed were as described in the first paper of this series (5).

OBSERVATIONS

Nucleus

The structure of the nucleus of the spindle-shaped sarcoma cells does not differ in its fundamental features from that of a normal fibroblast nucleus. The nuclei are large, oval, and regular in shape and possess a thin, pale membrane. The nucleoplasm is finely granular or reticular, the chromatin distributed in fine, dust-like particles. The nucleoli, single or double, are inconspicuous, and stain a pale blue with Giemsa's method.

The nuclei of the basophilic round cells are vesicular; their membrane is thick and not infrequently slightly wrinkled; the nucleoli are rather large; the basophilic chromatin is aggregated in several clumps; the nucleoplasm appears almost homogeneous.

The changes undergone by the nuclei of both spindle cells and basophilic round cells involve all the structural elements. The nucleoplasm is the seat of the most conspicuous alterations, and often acquires a more pronounced granular structure, appearing as if precipitated. The individual granules are more or less uniform in size and stand out distinctly against the almost colorless background. At first they are uniformly distributed throughout the nucleus but in time the granular material, indubitably originating from nucleoplasm, gathers in the central part of the nuclei. A more or less wide, distinct zone, a clear, unstained halo, becomes visible between the centrally located particulate masses and the nuclear membrane. In some preparations it may be perceived that this clear zone is traversed by extremely delicate, faintly staining threads, which run radially from the nuclear membrane towards the center. The granular material that collects in the central parts of the nucleus is always distinctly acidophilic. The nucleolus, surrounded by granular material, often retains its central position. In many cases, however, the nucleoli are pushed aside, and are found adjacent to the nuclear membrane. Occasionally the accumulation of particulate material occurs not in the center of the nucleus but in the form of a belt, which surrounds the nucleolus at some distance (Figs. 1 a and b).

Apart from these changes, processes taking place in the nucleoplasm frequently lead to the formation of structures of a different aspect. Many nuclei are found to contain round or ovoid, sharply outlined inclusions, mostly excentrically placed (Fig. 2). These stain bluish gray with Giemsa's method and blue with azan. Feulgen's reaction for thymonucleic acid gave negative results. These bodies appear at times uniform and homogeneous, at others they are vacuolated and may contain both denser and lighter areas. Usually they seem to be less dense than the nucleoli. The size of the inclusions varies. They may be minute and equal in size to average nucleoli, but at times they attain considerable size and then push the nucleolus aside. Generally only one such inclusion is found in a nucleus; more rarely there are two or more. Occasionally, however, nuclei packed with inclusions are encountered (Fig. 3). In some cases the inclusions are closely adjacent to the nucleolus, but as a rule there is

* Because of the difficulties of international communication the authors have not read proof of this article.

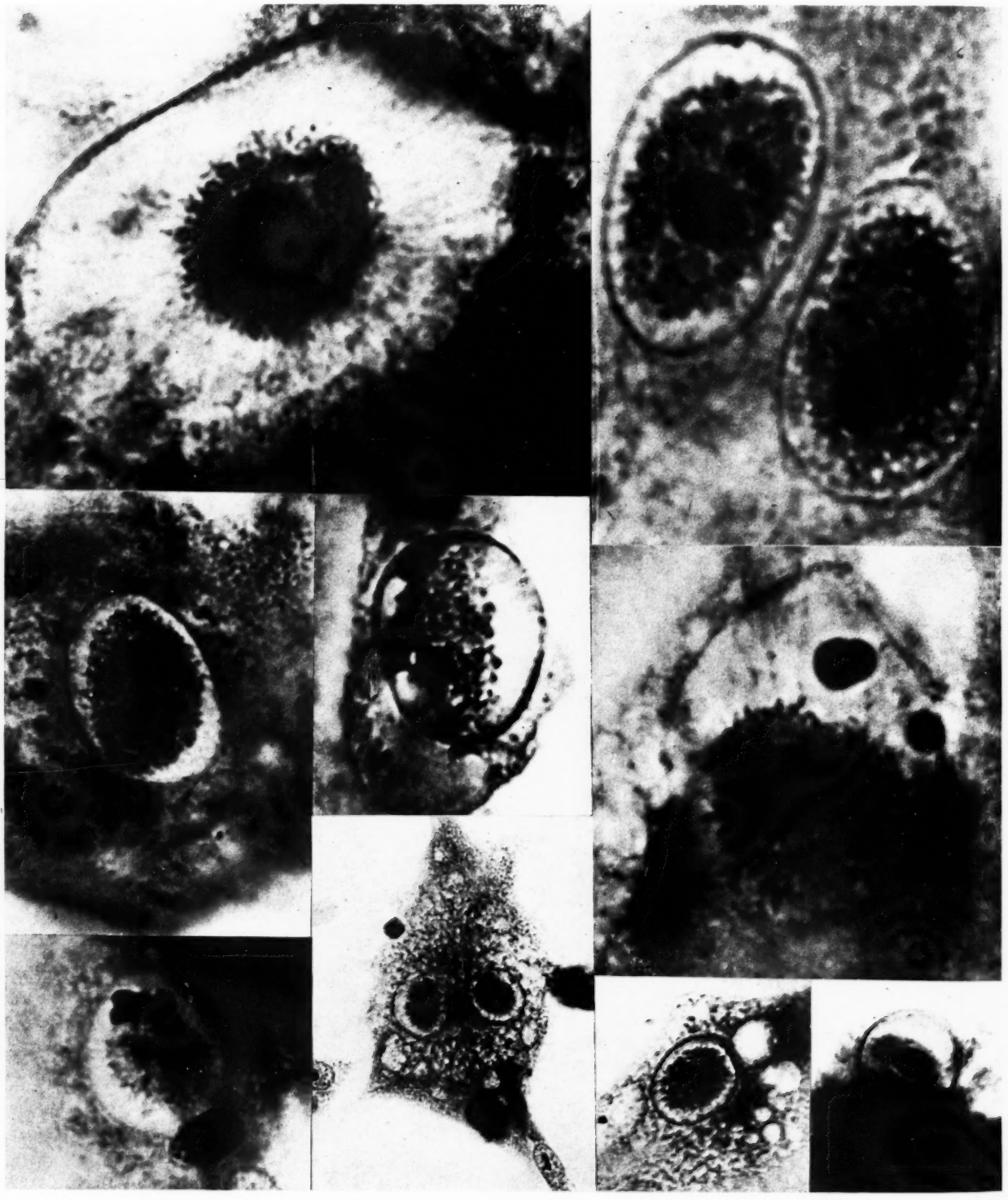

FIG. 1 a.—Central aggregation of eosinophilic particulate material in nuclei of Rous sarcoma cells. Giemsa stain. Mag. × 600 to 3,600.

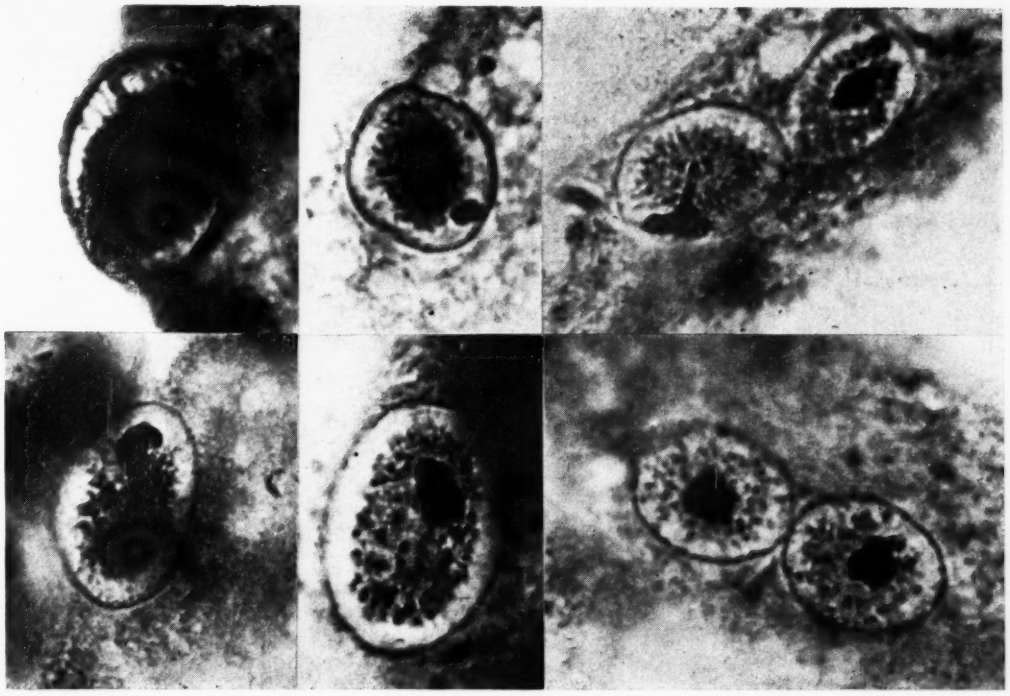

FIG. 1 b.—Central aggregation of eosinophilic particulate material in nuclei of Rous sarcoma cells. Giemsa stain. Mag. × 1,340 to 1,900.

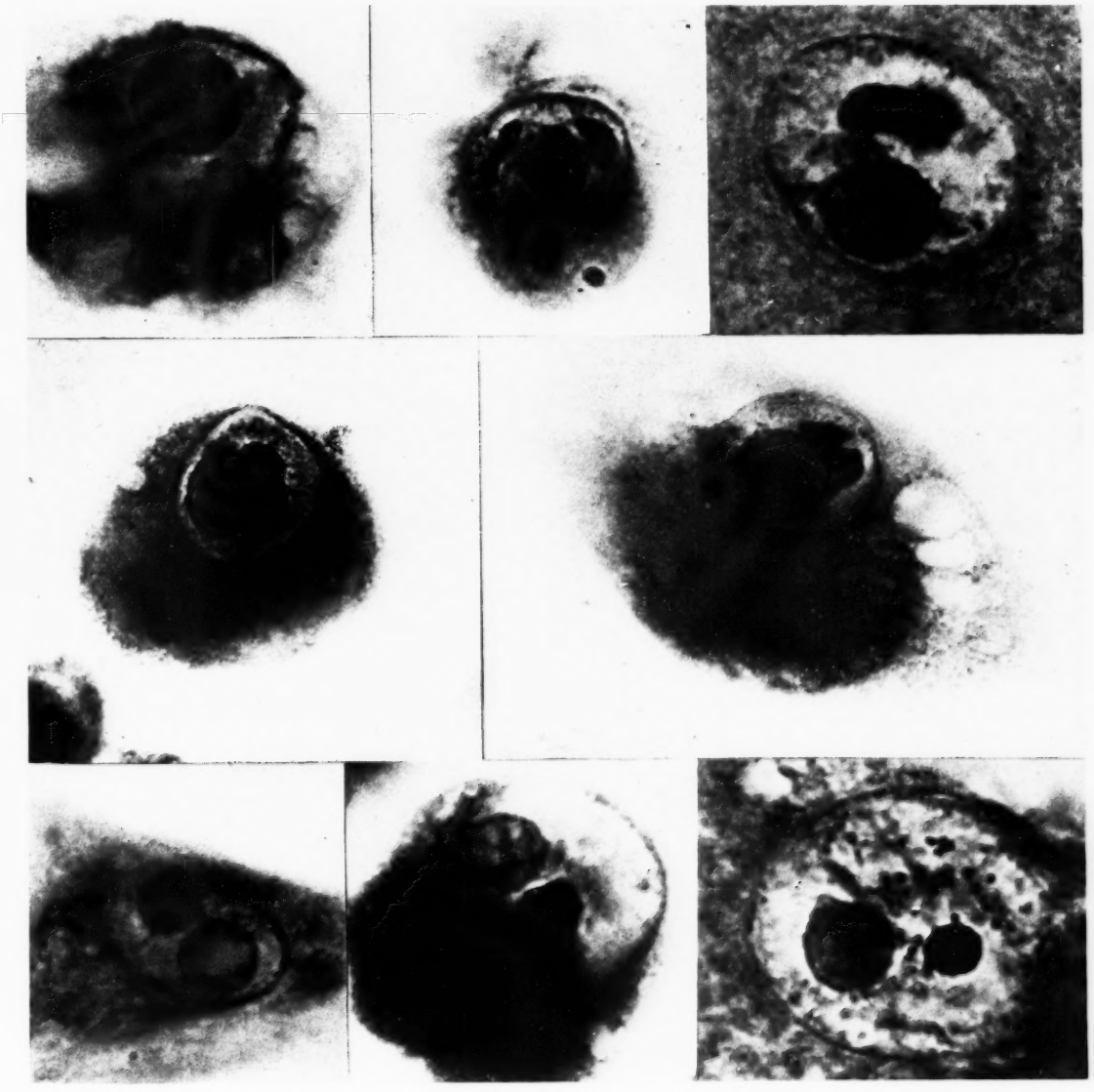

FIG. 2.—Spherical bodies in the nuclei of Rous sarcoma cells. Giemsa stain. Mag. × 660 to 2,640.

no obvious topographic relation between the nucleoli and the inclusion bodies. It may be noted that, in addition to the inclusions described above, sharply outlined vesicles or spherules are sometimes found within the nucleus. They generally appear to be empty, but at times contain a material very like that of which the inclusions are composed; moreover vesicles may be found that actually contain a well formed inclusion.

Both types of change affecting the nucleoplasm of a sarcoma cell are usually found to occur independently, but occasionally rounded inclusions and the central vacuoles in the nucleolus is very large, giving it an alveolar appearance. Now and then nucleoli are observed that stain deeply in the center and lightly at the periphery.

The basophilic chromatin of the altered sarcoma cell nuclei is rather sparse and aggregated in a few clumps. Margination of chromatin occurs, but is very rare. Frequently the nuclei appear vesicular, clear, and almost free of basophilic chromatin. Such nuclei are usually greatly enlarged, their sides often partly collapsed, and their center is without visible structure.

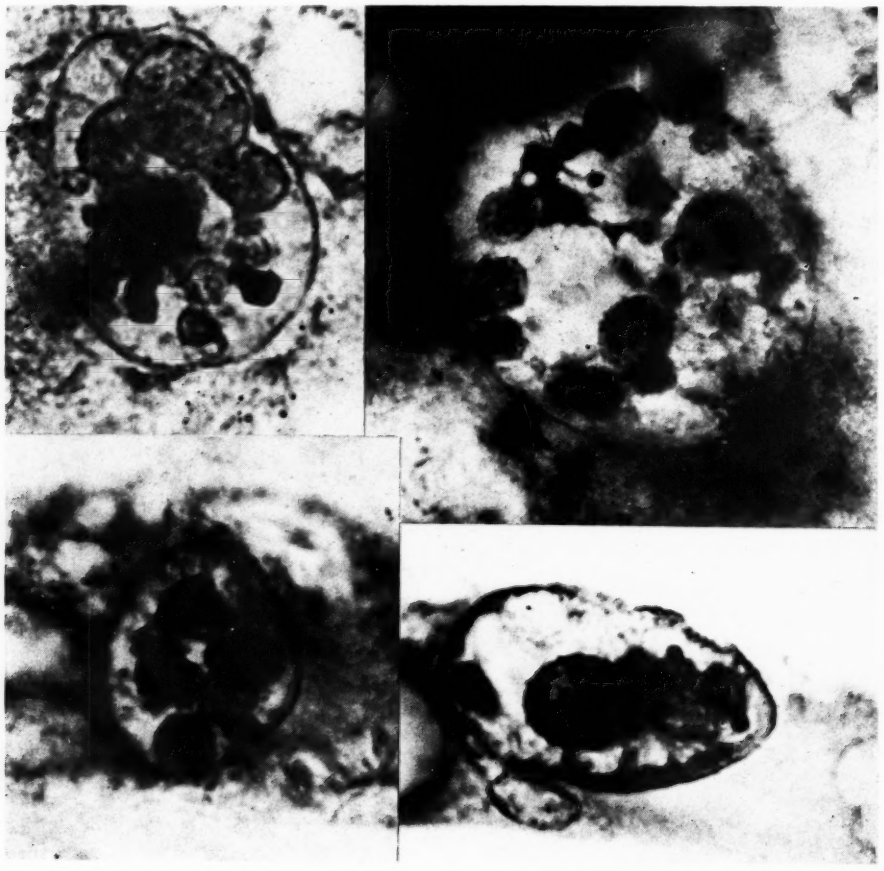

FIG. 3.—Multiple spherical bodies in nuclei of Rous sarcoma cells. Giemsa stain. Mag. × 990 to 1,800.

aggregation of oxyphilic granular material may be encountered combined (Fig. 4).

The nucleolus (Fig. 5) is almost without exception enlarged, appearing as a compact, deeply staining body. It may be round, oval, or rod-like in shape. Its position is mostly central, but when the cell changes are far advanced it is often shifted aside and may reach the nuclear membrane. At the height of the changes the nucleoli often become broken up into numerous fragments, which may be grouped together but more frequently are distributed throughout the whole nucleus. Very often nucleoli with one or a few minute vacuoles are encountered. Sometimes the number of

The nuclear membrane presents few peculiarities. In cells resembling fibroblasts it remains rather delicate and smoothly outlined, whereas in basophilic round cells it is thickened and sometimes slightly wrinkled.

CYTOPLASM

Like the nucleus, the cytoplasm of sarcoma cells cultivated *in vitro* undergoes a number of pronounced changes. Outstanding among them is the marking off of the central region of the cell from the remaining cytoplasm.

The segregation of the central zone of the cell is a

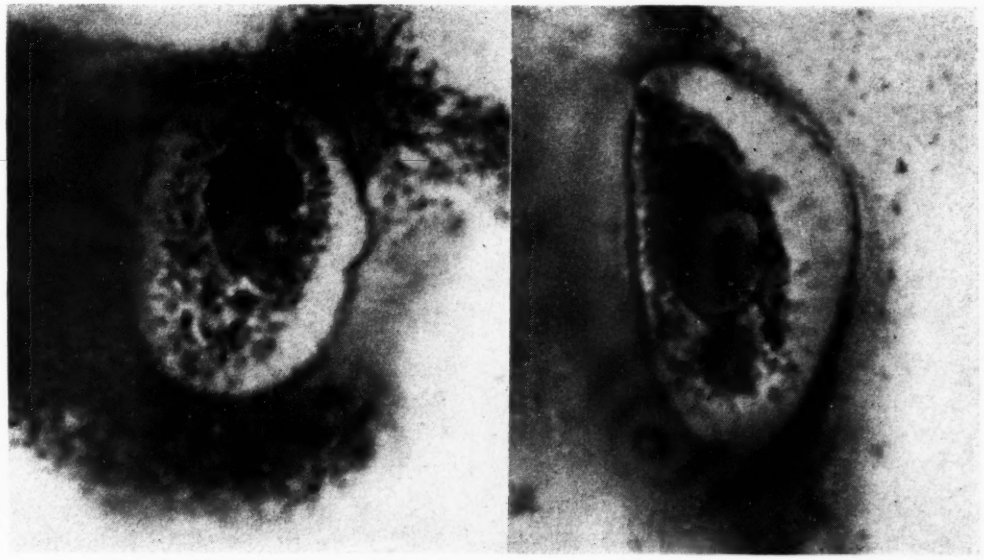

FIG. 4.—Aggregation of eosinophilic masses and spherical bodies in the same nuclei of Rous sarcoma cells. Giemsa stain. Mag. × 2,550.

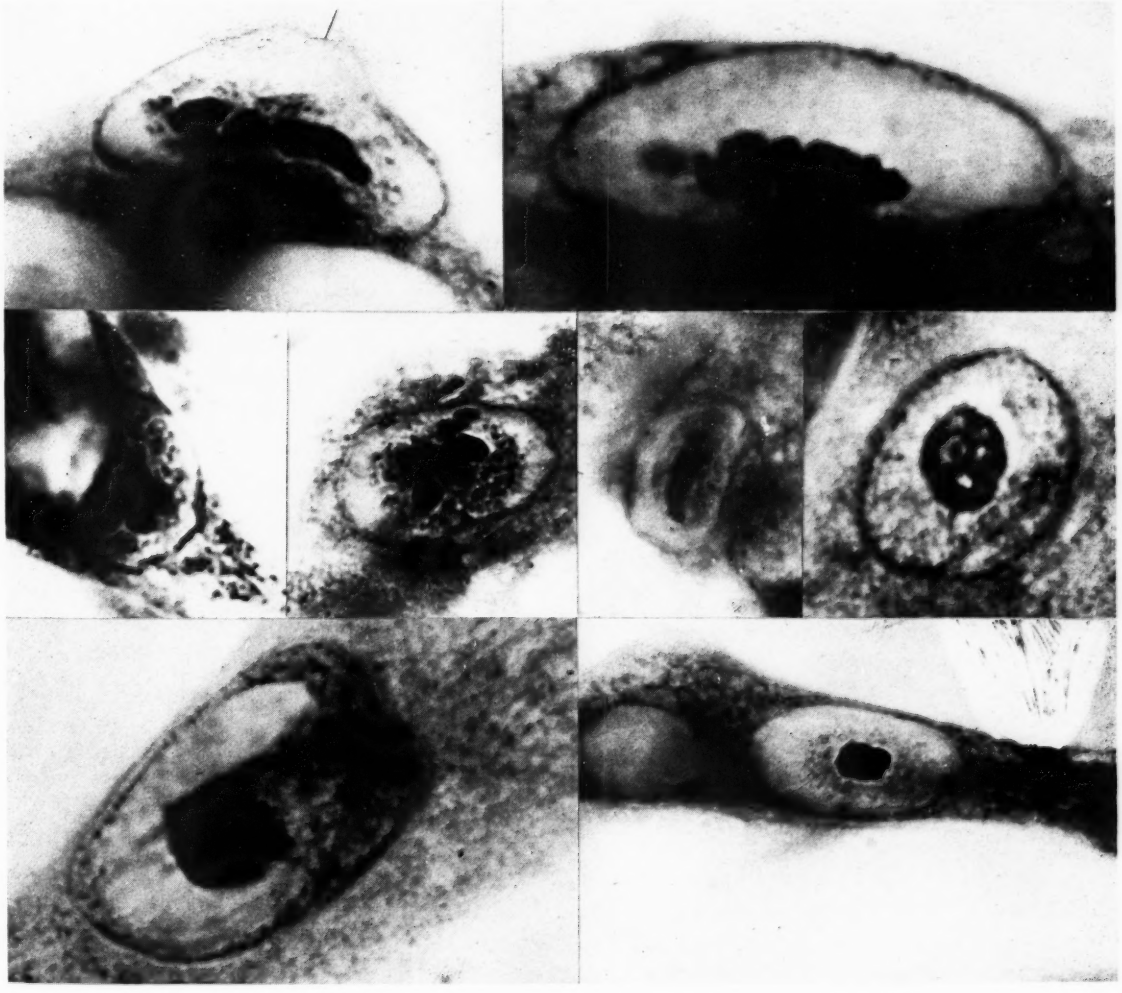

FIG. 5.—Nucleoli in Rous sarcoma cells. Giemsa stain. Mag. × 1,160 to 2,000.

process whose development may be followed step by step (Fig. 6). In its initial phase the central part of the cytoplasm takes on a cloudy appearance. Indefinite in the beginning, this zone gradually becomes better defined and finally assumes a sharp outline (Fig. 7). In general, the segregated central area is about 3 to 6 times as large as the nucleus. It is spherical in shape and always appears to be denser than the surrounding cytoplasm, but shows no pronounced structural peculiarities. The central area in the first stage of its development is always somewhat eosinophilic; in more advanced stages its tinctorial characteristics become rather indefinite; with Giemsa's method it stains at times reddish, at times bluish, but mostly in mixed tones. Its affinity for the dyes is always greater than that of the surrounding cytoplasm.

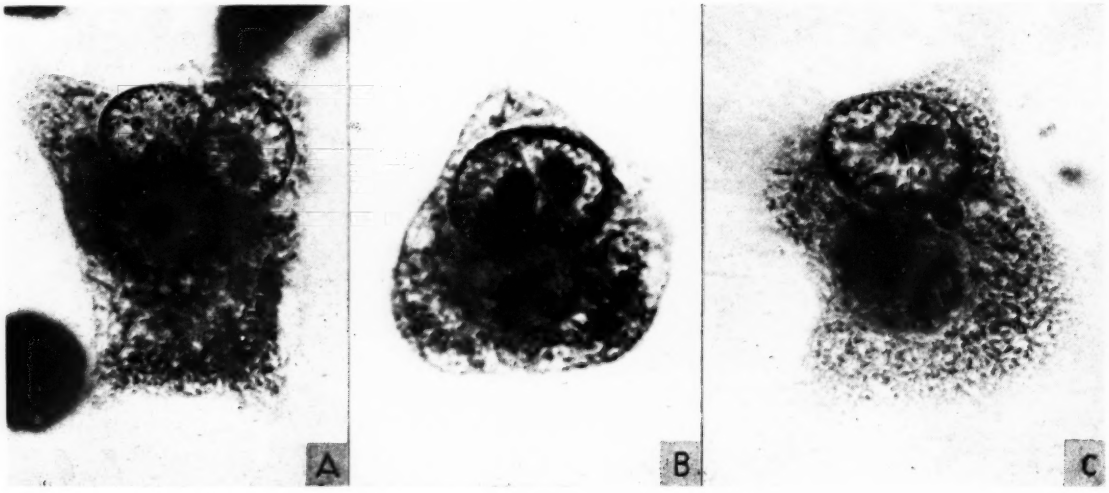

FIG. 6.—Early stages of segregation of the central area in Rous sarcoma cell. Giemsa stain. (a and c) Mag. × 1,140; (b) Mag. × 1,500.

The nucleus is almost invariably situated outside the central area, but as a rare exception it may be within (Fig. 8). In binuclear cells the central area usually lies between the two nuclei.

As a result of the segregation process, the sarcoma cell often appears to be built of two clearly distinct zones, central area and peripheral cytoplasm. The peripheral cytoplasm, too, presents striking peculiarities. It consists of a perfectly transparent, faintly staining, homogeneous ground substance that often contains strongly basophilic granules and thread-like structures. The granules are fairly uniform in size; the threads, which may be short and coarse, or delicate and branching, often form close networks.

The marking off of the peripheral from the central cytoplasm occurs most frequently in round cells; it may also be found in the spindle cells, and is fairly common in transitional forms. The peripheral cytoplasm of the spindle cells is devoid of pseudopodia. The ectoplasm of the large round cells, on the other hand, is pronouncedly motile. It possesses the character of a wide membrane, constantly changing in outline, but its vigorous movement never leads to significant displacement of the cell. Pseudopodia projected by these cells often have a very unusual aspect. They may appear as coarse, rigid rods that move in all directions on their base as on a joint. Their distal ends sometimes swell and become spherical (Fig. 9) and the protoplasmic masses so formed float on their flexible stems, often become detached, and retain their motility for some time (Fig. 10). Such ameboid cytoplasmic fragments, devoid of nuclei, are often encountered in considerable number, particularly in old cultures.

Frequently, though by no means regularly, the cytoplasm of the sarcoma cells contains numerous fine and coarse granules that stain intensively with eosin (Fig. 11). They may be found in different regions of the cells but generally exhibit a distinct preference for the peripheral layers of the cytoplasm. The outermost rim of the cytoplasm, however, almost always remains free of granules and surrounds the granule-laden zone as a narrow blue margin. Now and then the eosinophilic substance is found in gross clumps, which may be located paranuclearly or at the periphery of the cell (Fig. 12). They are often enclosed in a large vacuole. Invariably the eosinophilic substance is homogeneous in appearance. In a considerable number of preparations cells are encountered with cytoplasm pervaded by needle-shaped crystalline structures (Fig. 13).

The sarcoma cells are often rich in vacuoles. Some of the vacuoles stain with sudan III; others fail to show fat reactions. With neutral red the vacuole system is always clearly demonstrable, though the distribution of the vacuoles is peculiar. At times all the

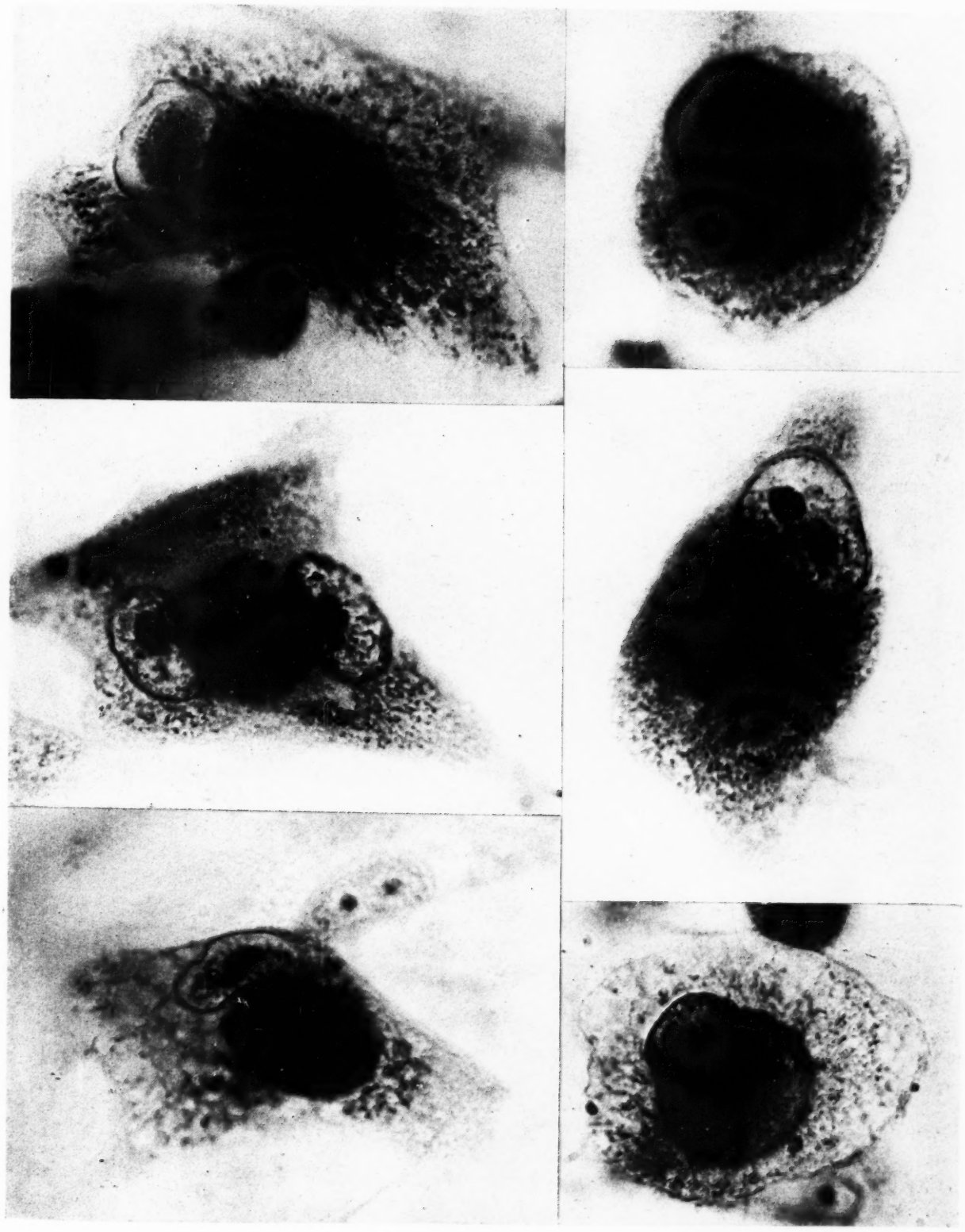

FIG. 7.—Segregated central area in Rous sarcoma cells. Giemsa stain. Mag. × 1,080 to 1,500.

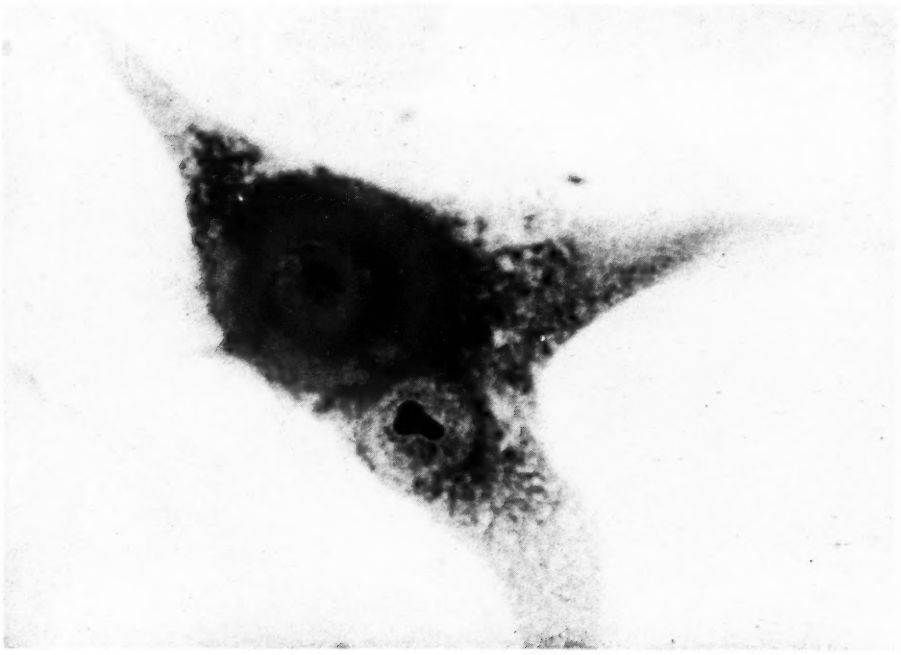

FIG. 8.—Segregated central area in Rous sarcoma cells. Giemsa stain. Mag. × 1,400.

FIG. 9.—Rous sarcoma cell with pedunculated spherical pseudopodia. Living. Mag. × 585.

peripheral cytoplasm is vacuolated and the central area almost free, in other cases the central area is rich in vacuoles and the peripheral cytoplasm free. The most usual localization of the vacuoles is at the bound-

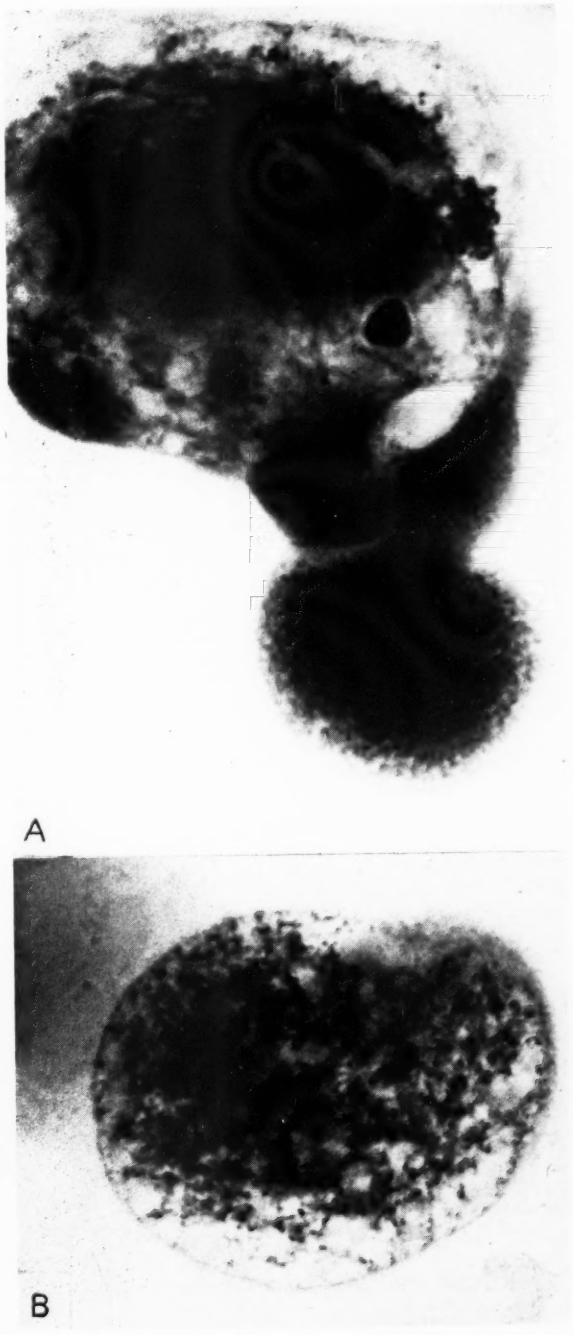

FIG. 10.—(a) Nipping off of spherical cytoplasmic masses. Giemsa stain. Mag. × 1,700.

(b) Spherical cytoplasmic mass free in plasma. Giemsa stain. Mag. × 1,415.

ary between the central and the peripheral cytoplasm; here they are more or less densely accumulated and often form a ring around the whole of the central area (Fig. 14).

Mitosis and Nuclear Fragmentation

Karyokinesis occurs frequently in sarcoma cultures (Fig. 15). This type of multiplication is common in both spindle and round cells, so long as the morbid changes are not advanced. In the course of time normal mitosis becomes increasingly rare, the mitotic coefficient falls, and atypical forms (reduced chromosome number, clumped and aberrant chromosomes, multipolar mitosis, etc.) appear.

Direct cell division is only rarely to be seen, but its occurrence is certain (Fig. 16). Nuclear fragmentation and budding not followed by division of the cytoplasm is, on the other hand, remarkably frequent (Fig. 17). The nuclei often split into two or more pieces, which vary greatly in size and may not be morphologically equivalent. Side by side with fragments of normal nuclear structure there occur others whose structure is incomplete; they may lack nucleoli or basophilic chromatin and may also appear entirely empty (Fig. 18). Nuclear fragmentation not followed by cleavage of the cytoplasm results in an unusually high number of binucleated or multinucleated cells.

In many sarcoma cells the size of the nucleus is in correspondence with that of the cytoplasm, but this is not the rule. Larger cells with one or several very small nuclei are often encountered. On the other hand small cells with remarkably large vesicular nuclei are in no way uncommon. The nucleocytoplasmic ratio *in vitro* thus appears to be highly variable.

Size and Shape of the Sarcoma Cell

One of the most striking features of the Rous sarcoma in cultures is the extremely wide variation in the size of its cells, the diameters of which run from 5 to 400 microns. This fluctuation in size notably exceeds that observed in cultures of normal cells. Basophilic round cells 5 microns in diameter and spindle cells 7 microns long and 23 microns wide on the one hand, and monster cells almost 0.5 mm. in diameter on the other hand are often encountered in sarcoma cultures, whereas cells of such dimensions are never found in cultures of normal mesenchyme cells.

This hypertrophy of sarcoma cells constitutes a peculiar phenomenon. Most of the hypertrophic sarcoma cells differ decidedly from the giant cells found in cultures of normal mesenchyme, for usually these are only broadened and flattened polynuclear syncytia. Sarcoma cells, on the other hand, show a true hypertrophy, preserving in every respect the architecture of their prototypes, the basophilic round cell and the spindle cell, and differing from the latter only in size (Fig. 19).

These two fundamental types remain distinguishable even at the height of development of the changes here

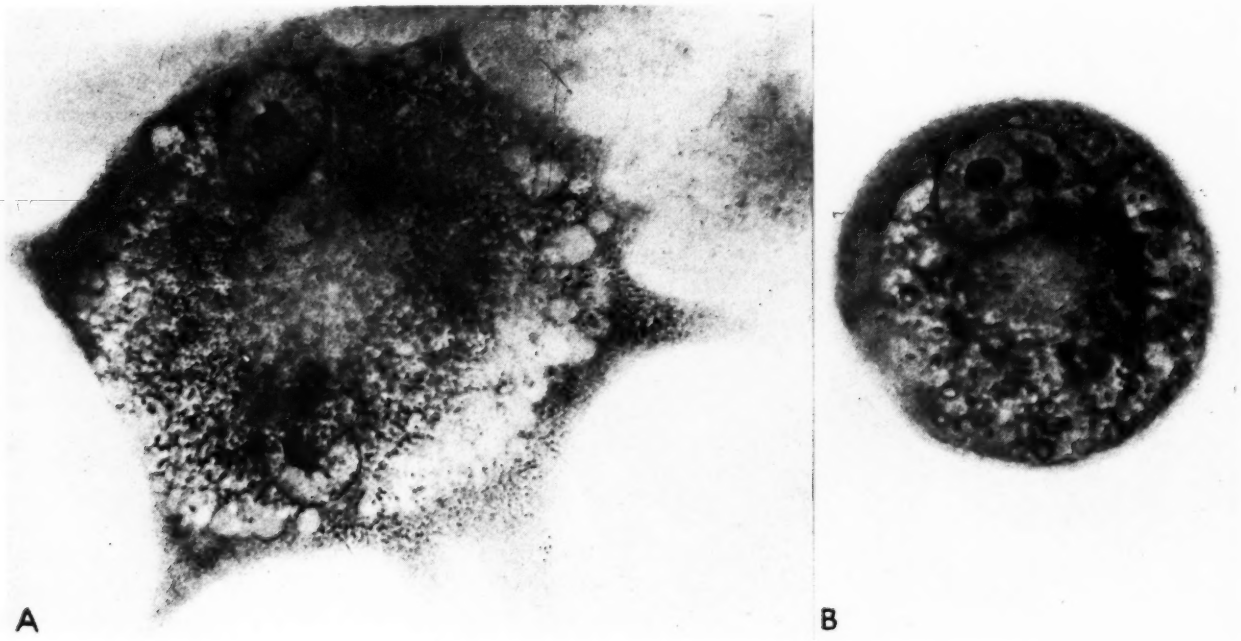

FIG. 11.—Eosinophilic granulations and droplets in cytoplasm of Rous sarcoma cells. Giemsa stain. (a) Mag. × 1,400; (b) Mag. × 680.

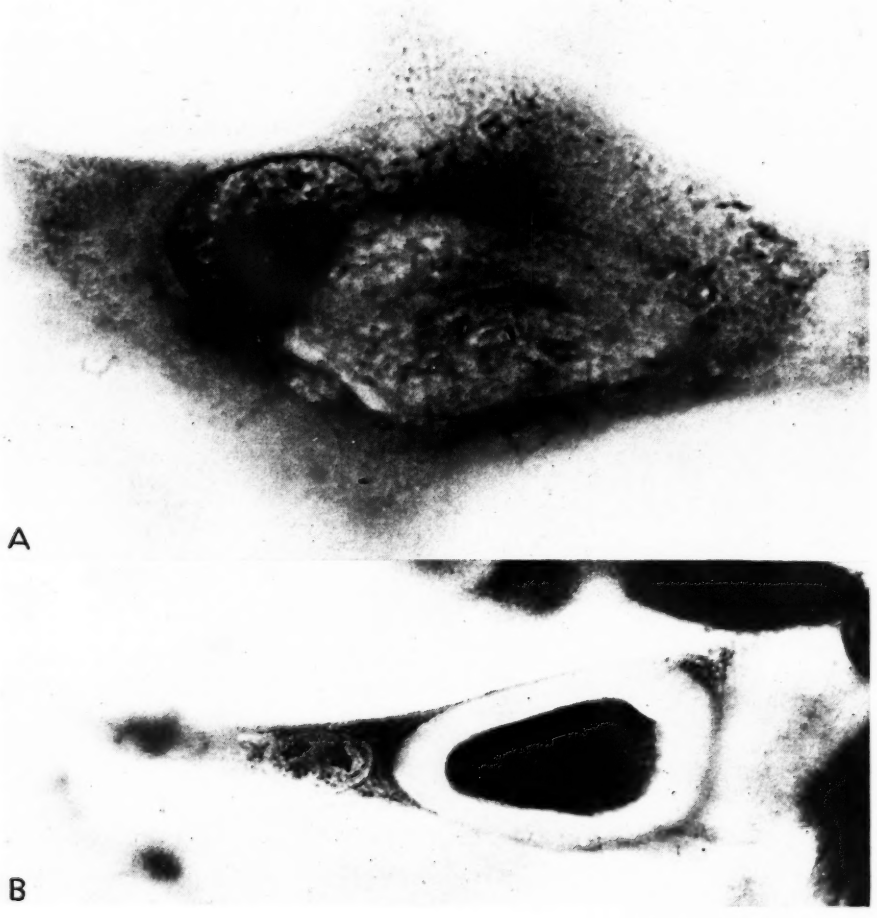

FIG. 12.—Eosinophilic masses in Rous sarcoma cells. Giemsa stain. (a) Mag. × 1,300; (b) Mag. × 680.

described. Transitional forms are also present, some possessing more of the spindle cell characteristics, others inclining more towards the round cell type, and this simultaneous occurrence of transitional forms and extreme cell hypertrophy leads to the formation of monstrous cell elements (Figs. 20, 21, and 22).

RESULTS AND DISCUSSION

Although the Rous sarcoma has been the subject of intensive study throughout the last three decades, our knowledge of the morphology of its cells is incomplete, and detailed investigations on its histological structure are lacking. Nor has the method of tissue culture contributed much toward elucidation of the structural characteristics of its cells. It is generally believed that in cultures the Rous sarcoma consists of two kinds of cells, spindle cells and macrophages, which morphologically do not differ essentially from normal cells. The structural peculiarities described by various investigators have not been accepted as significant.

Our findings on Rous sarcoma grown *in vitro* without the addition of normal cells have led us to a different conception. We find that the cells then develop peculiar structural features, undergoing important changes that advance progressively during cultivation. Although these changes are manifold, their combination constitutes a distinctive entity.

The feature principally responsible for the peculiar aspect of the cultures is a hypertrophy of the individual cells, which may proceed to the formation of cells of monstrous dimensions. These retain, nevertheless, the form and architecture of their prototypes, the basophilic round cell and the spindle cell. Side by side with enormously enlarged cells the cultures contain elements of unusually small sizes. This extraordinary variation strongly suggests that the regulative mechanism, which in normal cells regulates size within rather narrow limits, is profoundly disturbed. The great deviation from normal of the nucleocytoplasmic ratio is also possibly connected with this disturbance.

The presence of giant cells of a peculiar character in filterable chicken tumors was first noted by Rous and Murphy (20). They emphasized that giant sarcoma cells are "entirely different from those occurring about foreign bodies in the fowl or associated with avian tuberculosis. They may reach a diameter of 100 microns or more, and are usually oval, with one or two blunt processes, or forks, and a single large nucleus, features which give them a superficial resemblance to ganglion cells." The presence of particularly small cells in fowl sarcoma was first pointed out by Teutschlaender (26), who considers these small lymphocyte-like cells specific tumor elements and calls them *indifferente Blastemzellen*. Teutschlaender thinks them sufficiently small to pass through the pores of a Siegmund ultrafilter. In cultures, the remarkable variations in the size of sarcoma cells was first noted by Fischer (9). He described small cells corresponding in size to bacteria side by side with cells 50 to 150 times as large. Borrel (2) found that multinuclear sarcoma cells adhering to the bottom of culture flasks may reach diameters of 600 microns.

Next to the phenomenon of cell hypertrophy, changes in the nuclei deserve emphasis. In many cells granular eosinophilic material of nucleoplasmic origin

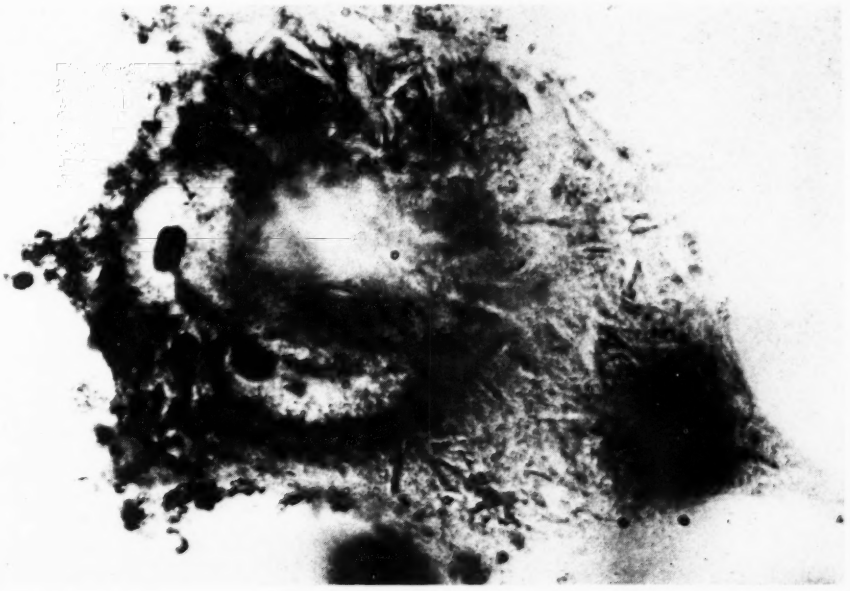

FIG. 13.—Crystalline structures in Rous sarcoma cells. Giemsa stain. Mag. × 1,060.

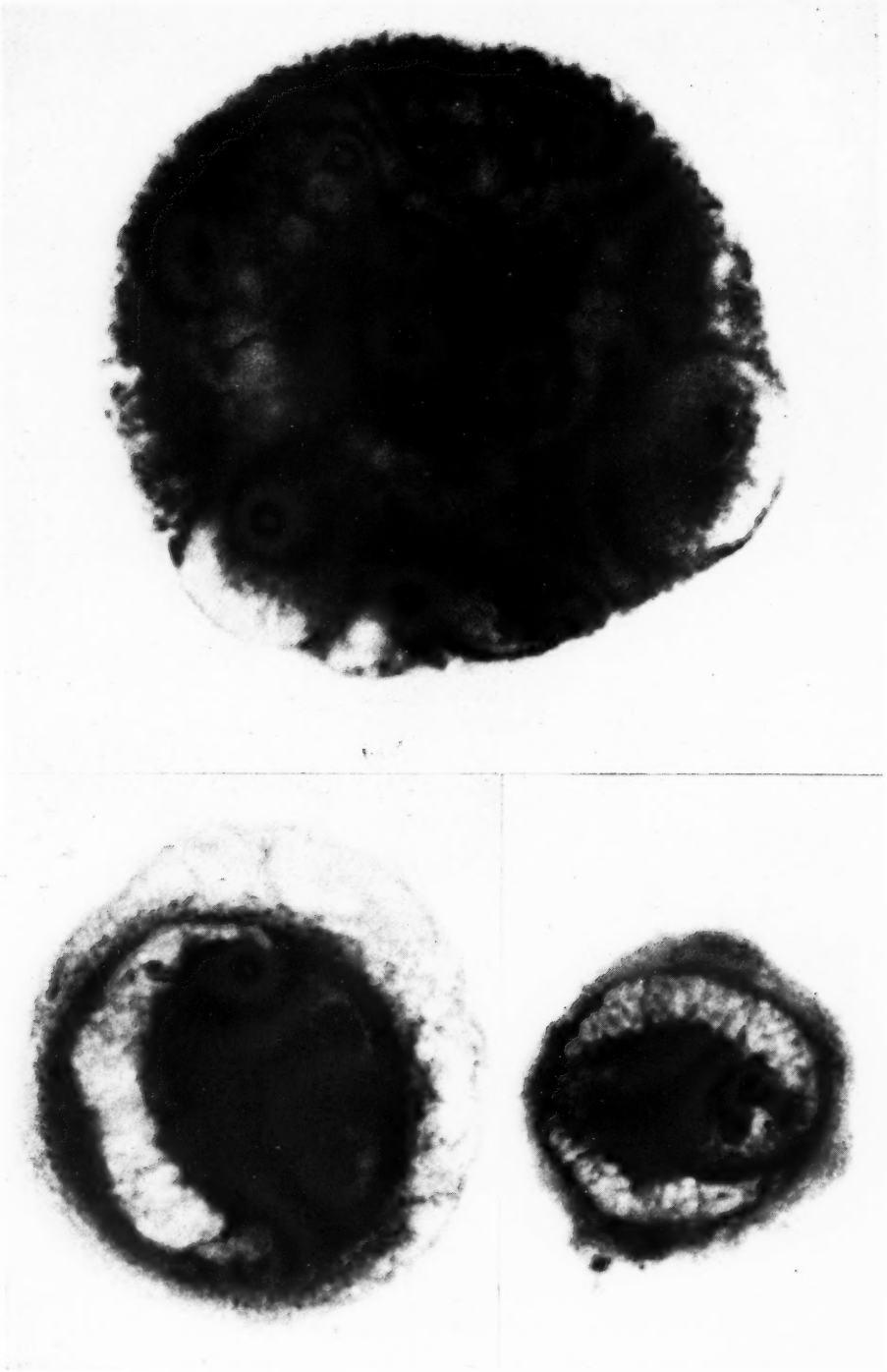

FIG. 14.—Vacuolated Rous sarcoma cells. Giemsa stain. Mag. × 1,800.

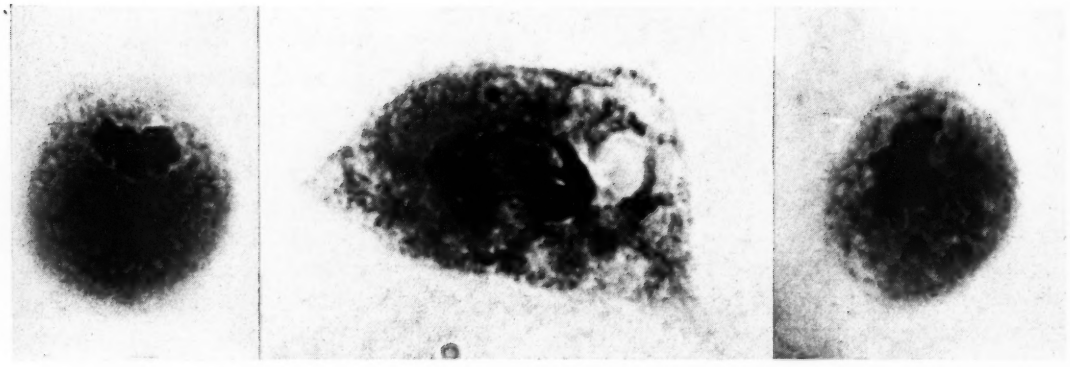

FIG. 15.—Mitosis in Rous sarcoma cells. Giemsa stain. Mag. × 1,400 to 1,700.

accumulates in the central part of the nucleus, leaving a characteristic area of rarefied nucleoplasm between it and the nuclear membrane. In addition, clearly defined small, rounded, homogeneous, intranuclear inclusions that stain bluish gray with Giemsa's method are found in many sarcoma cells. The nucleoli are often hypertrophic and, with progress of the cell changes, may be pushed aside and broken into irregular fragments that either scatter throughout the nucleus or gather toward the center or the periphery. Often the nucleolar substance contains single or numerous minute vacuoles. The entire nucleus becomes vesicular and almost free from basophilic chromatin. It is often extremely lobulated.

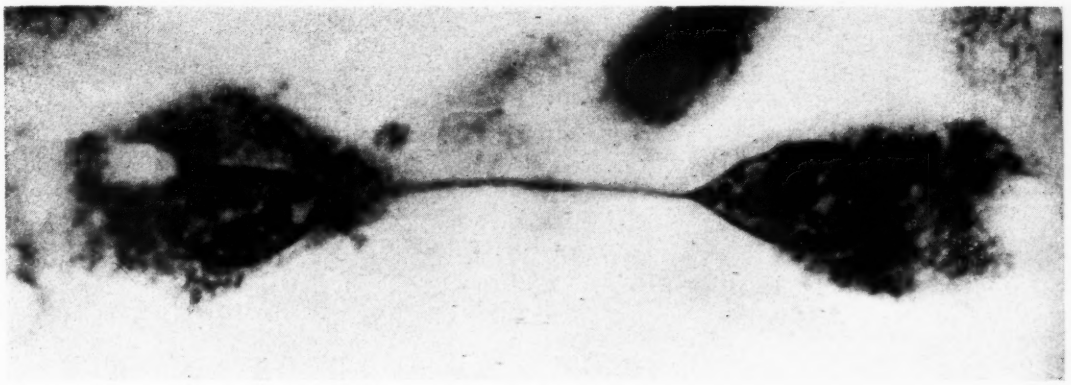

FIG. 16.—Amitosis in Rous sarcoma cell. Giemsa stain. Mag. × 2,680.

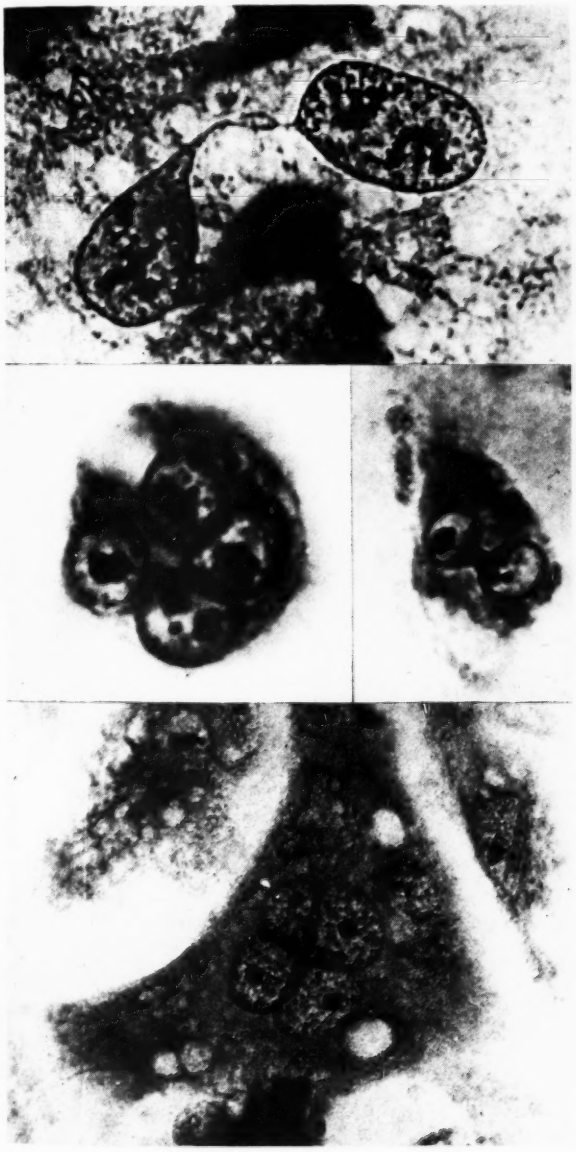

FIG. 17.—Nuclear fragmentation in Rous sarcoma cells. Giemsa stain. Mag. × 1,600 to 1,900.

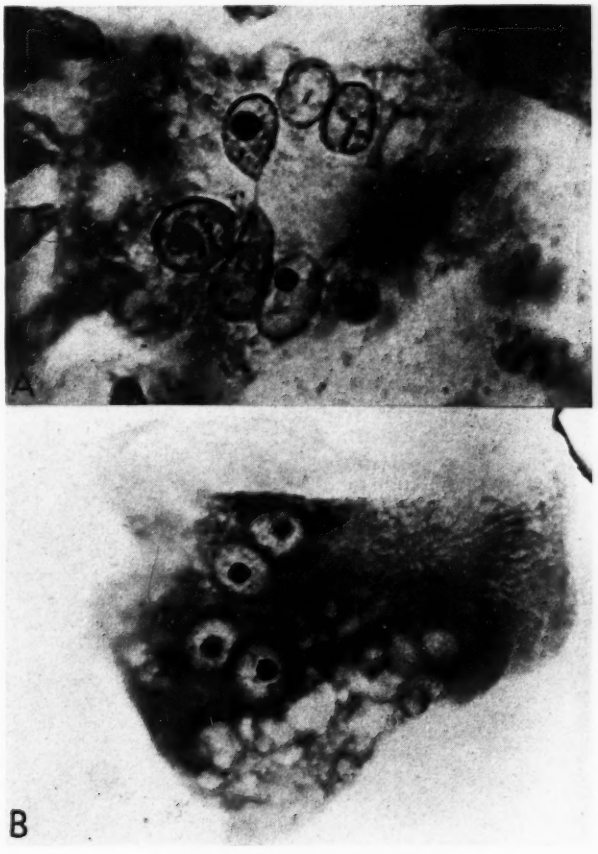

FIG. 18.—Fragmented nuclei in Rous sarcoma cells. Giemsa stain. (a) Mag. × 1,400; (b) Mag. × 1,200.

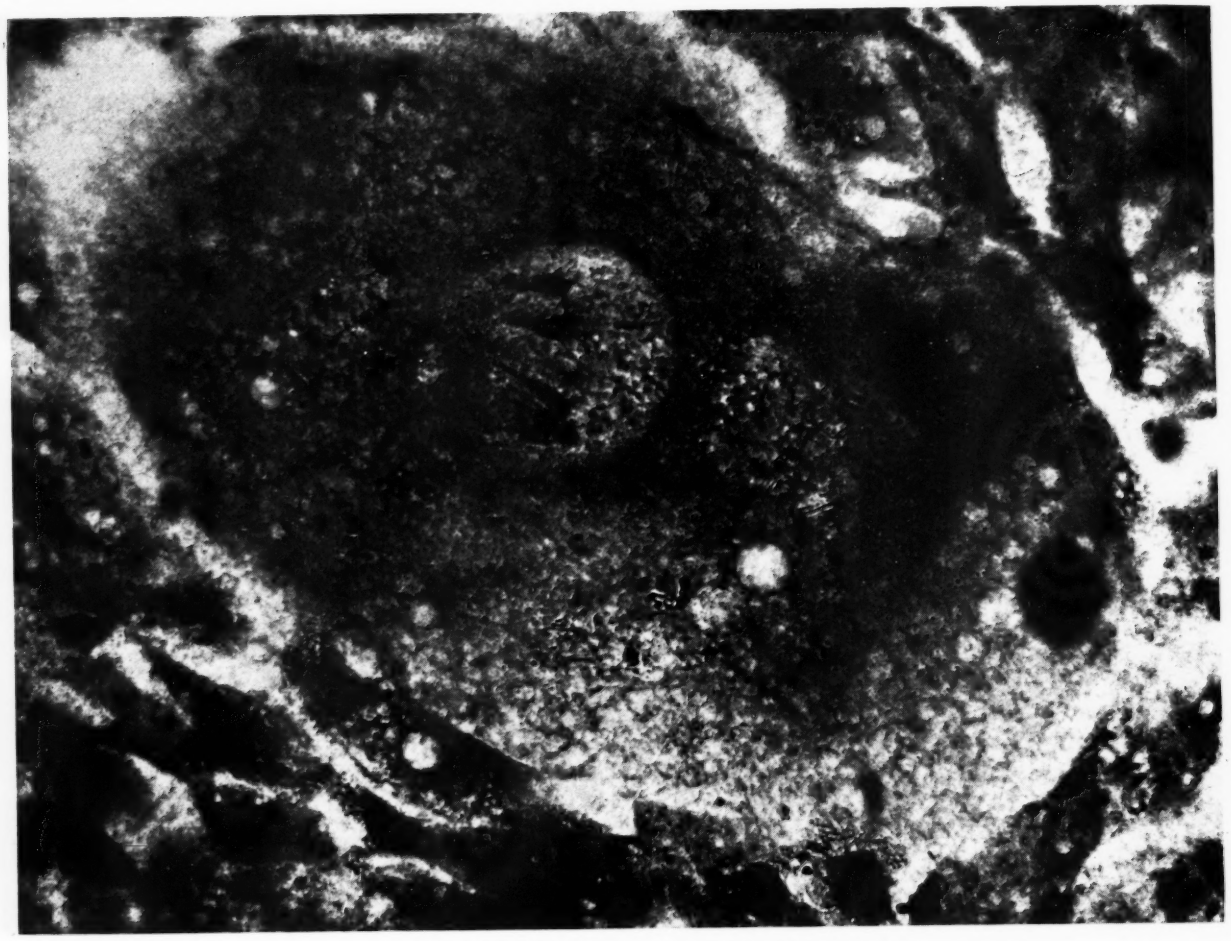

FIG. 19.—Hypertrophied Rous sarcoma cell. Mag. × 540.

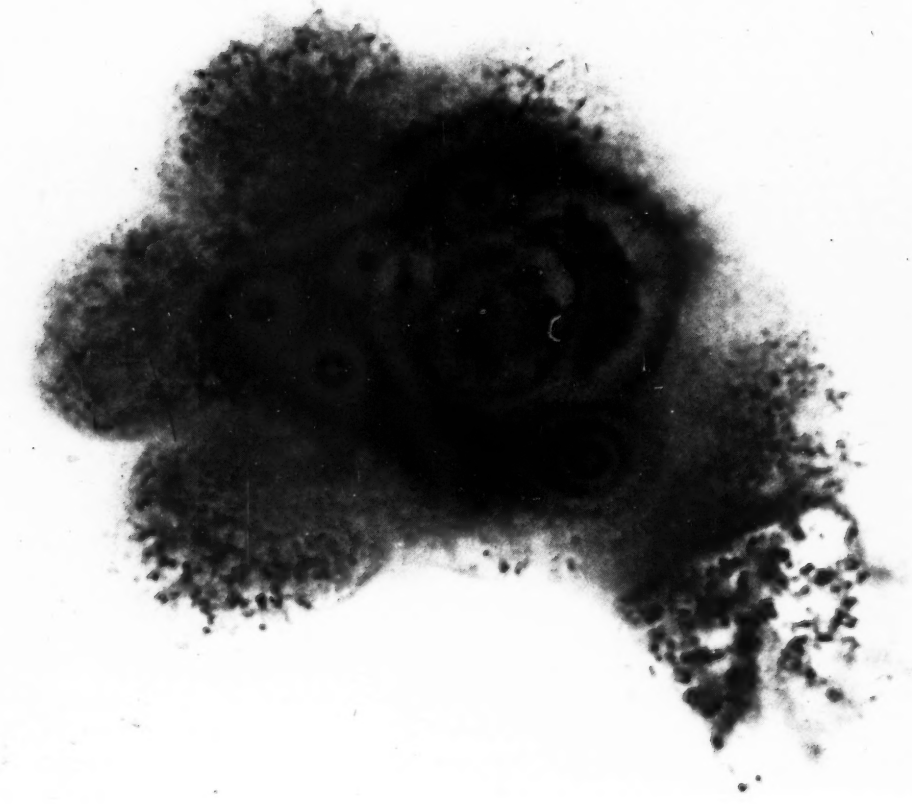

FIG. 20.—Rous sarcoma cell. Giemsa stain. Mag. × 1,790.

Intranuclear inclusions have not so far been described in cells of the Rous sarcoma, though in spontaneous round cell sarcomas of chickens Sanfelice (22) noted

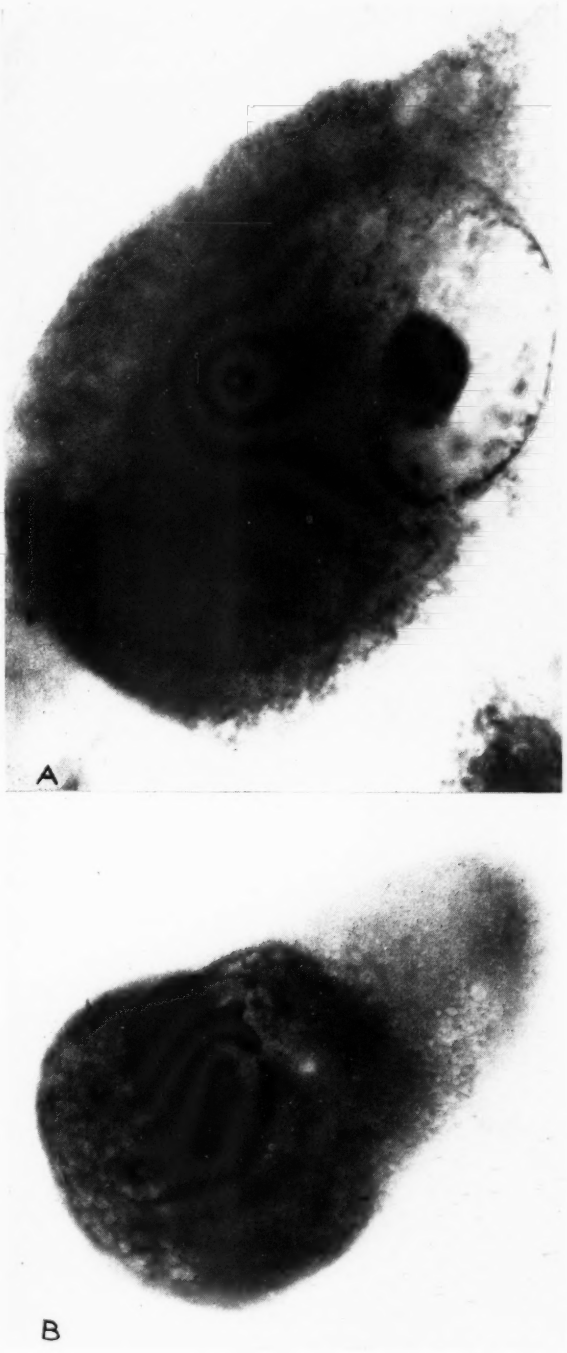

FIG. 21.—Rous sarcoma cells. Giemsa stain. (a) Mag. × 785. (b) Mag. × 1,750.

small eosinophilic inclusion bodies of irregular outline within the nuclei.

Rous and Murphy (20) stated that the single nucleus of chicken sarcoma cells is often excentrically placed and sometimes pyknotic, "but more often vesicular and swollen, with its chromatin in a central mass (fish eye nucleus)." According to Zweibaum (28), the nucleus of sarcomatous macrophages is optically completely empty and the nuclear membrane absent.

Fischer (8) described the nucleoli of sarcoma cells *in vitro* as "irregular formations." Zweibaum reported that whereas normal macrophages regularly contain one or two nucleoli that stain with acid dyes ("plasmosomes"), such are not found in the nuclei of sarcoma cells.

Not only the nucleus, but also the cytoplasm of Rous sarcoma cells is decisively disturbed. The most striking of the cytoplasmic alterations is a marking off of the central zone, which results in the formation of a roundish area at the center of the cell that differs from the remaining cytoplasm by its denser structure and deeper staining. The peripheral cytoplasmic layer of the cells involved exhibits certain peculiarities in structure and behavior. It often contains basophilic thread-like and granular structures that sometimes form extensive nets. In addition, one frequently finds within the cytoplasm eosinophilic material in the form of fine granules and clumps. In a few of the cells crystalline structures also are encountered. Vacuoles are present in abundance. Their peculiar distribution is, we believe, due to the fact that the cytoplasm is not uniform in composition. Corresponding to its heterogeneous structure the distribution of the vacuoles is not diffuse but regional, being restricted to the central or peripheral regions or, most often, to the boundary region between the two. The uncommon shape of the pseudopodia and the nipping off of large spherical masses of cytoplasm undoubtedly reflect deeper changes in the physicochemical state of the ectoplasm of the sarcoma cells involved.

Differentiation of the cytoplasm into two regions such as we have seen in cultures of the Rous sarcoma, was adequately described by Roskin (18) in sections of this tumor. He observed that after staining with Mallory's connective tissue stain or eosin-phloxine-water blue, the cytoplasm appears to consist of two sharply distinguishable layers: one external and transparent, and the other central and dense. According to Roskin the nucleus lies within the inner zone. Lipschütz (15), too, noted that the central region (archoplasm) often acquires properties that clearly distinguish it from the remainder of the cytoplasm. Borrel (2), Fischer (8), and Zweibaum (28) all have stated that the central area of sarcoma cells cultivated *in vitro* differs in its properties from the peripheral cytoplasm, but neither the description nor the figures of these authors indicate definitely whether the structures they observed were essentially similar to those seen by us. Zweibaum states explicitly that a central zone comparable to that observed in sections by both Roskin and Lipschütz is not evident in cultures. With regard to the cyto-

plasmic structures, Borrel (2) notes that the mitochondria of sarcoma cells are thread-like or filamentous, and that in enlarged cells enormous hypertrophy of the mitochondria occurs. Zweibaum emphasizes that in the macrophages of the sarcoma the mitochondria are more numerous and more filamentous and stain less intensely than in normal macrophages.

Eosinophilic granules in cells of the Rous sarcoma were seen by Borrel but could not be found by Zweibaum. Certain peculiarities in the distribution of vacuoles in the sarcoma cell in culture are referred to by Fischer (9). Lipschütz (15) noted, in addition to the basophilic structures described by him as "plastin reaction," certain characteristically distributed chromophobe vacuolar bodies, "stegosomata," which he believed to be specific for sarcoma cells. This was not confirmed by Caccia (3), Liégeois (14), or Schiller (23). The structures called "stegosomata" and the vacuoles that we have described are probably identical, so far as can be judged from the figures given by Lipschütz.

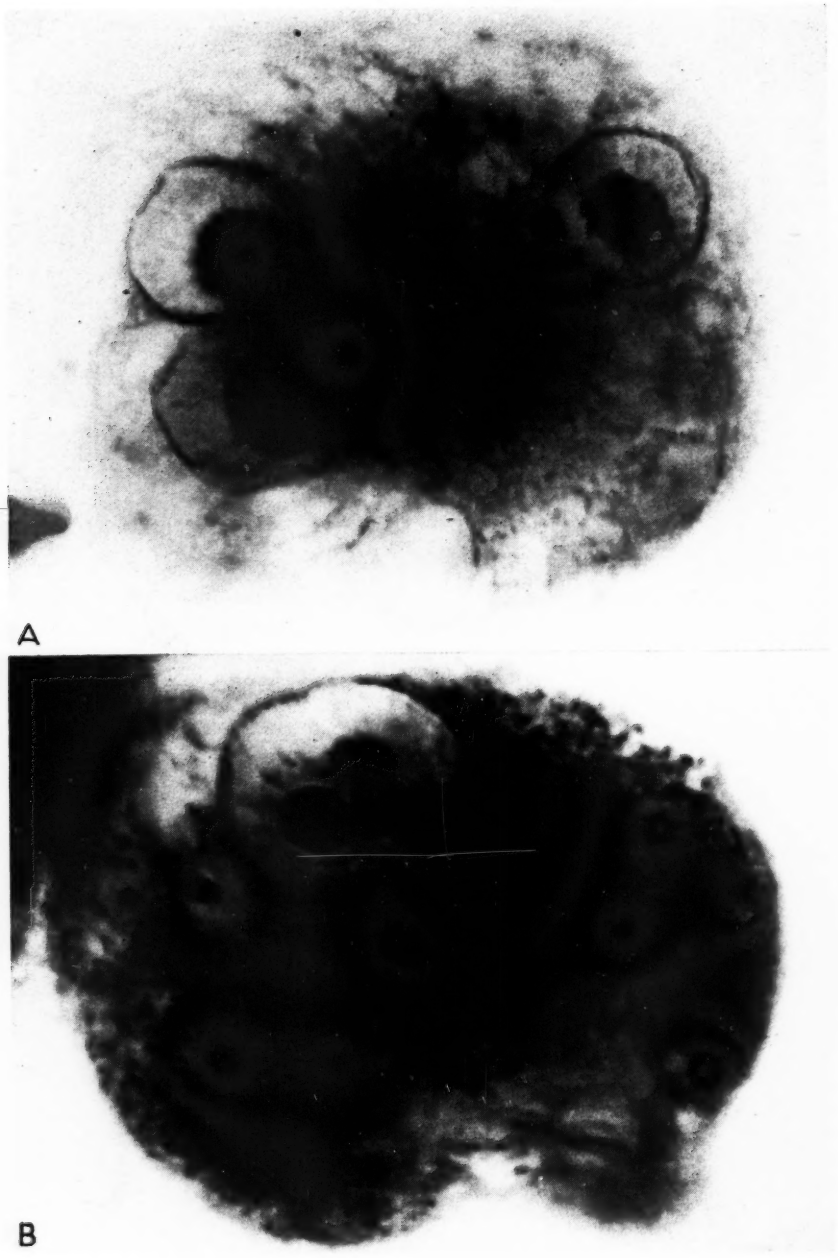

FIG. 22.—Rous sarcoma cells. Giemsa stain. (a) Mag. × 2,360; (b) Mag. × 1,600.

Mitoses are frequent in cultures of sarcoma cells and are encountered in both round and spindle cells. The mitotic coefficient falls and atypical mitosis ap-

pears as the cell changes advance. Nuclear fragmentation, which is not followed by cleavage of the cytoplasm, is very frequent. True amitosis also occurs.

The mitosis of sarcoma cells has been seen in sections by many authors, Rous and Murphy (20), Levine (12), and others. In cultures, on the other hand, mitotic cell division has been described as rare by Fischer (9) and as absent by Zweibaum (28), and the former discusses the possibility that sarcoma cells may multiply by fragmentation into several parts (amitosis?).

In interpreting the alterations undergone by the Rous sarcoma cell *in vitro* consideration should be given to the fact that this cell is associated with a virus-like pathogenic agent. It is relevant, therefore, to inquire whether and in what degree the changes observed correspond in character with those known to be caused by viruses.

In this connection two phenomena deserve special consideration: the nuclear changes and the cellular hypertrophy.

The nuclear alterations present certain points of similarity to changes occurring in virus infections and generally considered highly pathognomonic. The aggregation of oxyphilic granular material in the central part of the nuclei, separated from the nuclear membrane by a characteristic area of unstained and rarefied nucleoplasm, resembles closely those changes in the nuclei of virus-infected cells that Cowdry (4) has classified as type A inclusions. The spherical bodies found in the nuclei are comparable in many respects to the type B inclusions of Cowdry's classification.

Although this resemblance is obvious, it is by no means complete. In the nuclear changes here described as similar to type A inclusions, the general structure of the affected nuclei is often not disturbed. Side by side with cells in which the nucleoli are pushed aside, others with inclusions are frequently found in which the nucleoli retain their central position. Basophilic chromatin in most instances fails to marginate to the nuclear membrane. The oxyphilic masses are never condensed into homogeneous bodies. The conformity of the second variety of nuclear change here described with type B inclusions is imperfect, above all because an outstanding though not obligatory characteristic of B inclusions, eosinophilia, is not present.

In addition to the changes described above, the nuclei of Rous sarcoma cells display other definite modifications such as fragmentation and disintegration of the nucleoli, disappearance of basophilic chromatin, extreme lobulation and budding at times, that further accentuate the resemblance of the changes undergone by these nuclei to the nuclear changes caused by viruses.

But the evidence that they are a result of virus action is by no means conclusive. It should be noted that the nuclear inclusions have been found not only in virus tumors as, for example, the transplantable adenocarcinoma of the frog's kidney studied by Lucké (16, 17), but also in mammalian tumors, where etiological relation with a virus is highly uncertain. The occurrence of intranuclear inclusion bodies has been noted in various human brain tumors by Russell (21) and by Wolf and Orton (27), and in carcinoma of the thyroid gland by Stewart (25). In this laboratory, intranuclear inclusions closely resembling the type B inclusions here described, have been observed recently in nuclei of sarcoma in man. Apitz (1) saw alterations of a somewhat similar kind in the nuclei of melanotic tumors, describing them as "vacuolar degeneration." Fischmann and Russell (10) reported intranuclear inclusions in cultures of human fetal leptomeninges, as well as in cultures from the leptomeninges of rat and chicken embryos, and in fibroblast cultures from the lungs of human and chick fetuses.

Thus it must be emphatically stated that no definite conclusions can be drawn at present on the etiological significance of intranuclear inclusions. Inclusion bodies had been reported in various conditions in which viruses are apparently not involved, and the presence of intranuclear inclusions cannot, therefore, be taken at face value as indicating the action of a filterable virus. In the words of Cowdry (4), "They may be simply the expression of nuclear modification, occurring not only in some virus diseases, but also in many conditions for which viruses are probably not responsible."

In regard to the hypertrophy of the sarcoma cells the following may be observed. Hypertrophy is a common response to the presence of a virus, and it is of interest to note, therefore, that in cells bearing the Rous agent true hypertrophy is constantly encountered and often attains extreme degrees. It is unjustifiable, however, to regard this as an absolute indication of virus action for hypertrophy is by no means a specific cell reaction. Fell and Andrews (7), for instance, describe hypertrophy in cells of the Jensen rat sarcoma cultivated *in vitro,* not so pronounced in degree but similar to the type seen by us in cultures of the Rous sarcoma.

The nature of the cytoplasmic modifications is most uncertain. None of the changes in the cytoplasm here described can be considered as indicative of virus action.

The segregation of the cytoplasm into two distinct zones, central body and peripheral cytoplasm, is not characteristic of virus infection. The marking off of the central cell region, so pronounced in cells of the Rous sarcoma, has been noted, though in less degree,

in normal cells and in cells of mammalian tumors also. Lewis (13) pointed out that the central region in degenerating mesenchyme cells can become hypertrophied and then presents itself as an area that is sharply delimited from the remaining cytoplasm ("giant centrospheres," "central bodies"). He suggests that the hypertrophy of the central zone is evidence of disturbed cell metabolism. Fell (6) described a similar phenomenon in hypertrophied chondroblasts. Hypertrophy of the central region has been observed also in cultures of Jensen rat sarcoma cells by Fell and Andrews (7) and by Hirschfeld and Klee-Rawidowicz (11), and Smith (24) noted a similar change in cultures of xanthomatous tissue.

The net-like basophilic structures in the cytoplasm of sarcoma cells, which resemble hypertrophied mitochondria, are likewise by no means specific. According to our observations, basophilic filaments and granules can be observed at times also in normal macrophages fixed in Carnoy's solution and stained by the Giemsa method. The difference between normal cells and those of the Rous sarcoma in this respect is only quantitative.

On the other hand, the acidophilic droplets and deposits of acidophilic masses found in the sarcoma cells are unknown in normal cells. The granules that develop in the cytoplasm of degenerating macrophages and fibroblasts are of a different character, even though they, too, at times stain an intense red with Giemsa's method. Borrel's view (2) that the eosinophilic substance is a specific product of the Rous sarcoma cell, is, nevertheless, by no means proved.

The peculiar behavior of the peripheral cytoplasm of sarcoma cells, that is to say the unusual aspect of the pseudopodia and the nipping off of spherical protoplasmic masses, is, as has been mentioned above, indubitably a sign of some profound disturbance in the physicochemical state of the cytoplasm. But the question whether these changes are a direct outcome of the activity of the causative agent must remain open. Summarizing, then, we may say that cells of the Rous sarcoma display *in vitro* a number of definite modifications. Some of the latter resemble in certain important ways alterations known to us as "fingerprints" (Cowdry) of virus action; others are of a totally nonspecific character. Together they constitute a remarkable morbid picture, a distinctive syndrome of a severe cell disease.

It can hardly be doubted that its etiologic factor is the filterable agent of the Rous sarcoma. A definite argument in favor of this conception will be given in our next communication, where it will be shown that the changes developing in normal mesenchyme cells infected with the Rous agent *in vitro* are identical with those here described. In what manner the agent is involved in the changes observed, which of these can be looked upon as a direct and which as an indirect outcome of its action, is a question that does not lend itself to discussion at the present time. The fact, however, that some of the changes observed in cells of the Rous sarcoma resemble alterations known to be indicative of virus infection appears to us worthy of consideration, especially in view of the fact that the virus nature of the Rous agent is still under discussion.

In the present paper we have reviewed the various cell changes that occur in cultures of the Rous sarcoma, without considering the chronological sequence in which the changes appear, the manner in which they combine, or the degree to which they involve the cells at different stages in the development of the culture. We intend to give later a description of the evolution of these alterations, and to show that the degenerative and hyperplastic changes that constitute the morbid syndrome here presented are ultimately lethal.

SUMMARY

The alterations undergone by cells of the Rous sarcoma growing *in vitro* are described and illustrated. The nature and significance of these changes are discussed.

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Further Observations on Skin Carcinogenesis by a Single Application of 20-Methylcholanthrene*

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The induction of skin cancer in a fraction of mice treated by a single application of a potent carcinogen—methylcholanthrene—has been demonstrated so far in two strains: the C57 brown strain used by Mider and Morton (2), and the Swiss strain used by Cramer and Stowell (1). A negative result was reported by Mider and Morton with C57 black mice (3). This note records the positive carcinogenic response to similar treatment with methylcholanthrene in New Buffalo mice, the third strain to be reported susceptible.

The experimental technic was the same as that used by Cramer and Stowell (1): a 0.6 per cent solution of the carcinogen applied on one occasion only to a large area of the back by means of 3 strokes of a No. 4 camel's hair brush. In 12 effective mice (mice alive when the first tumor appeared) 3 malignant growths developed, 2 carcinomas and one sarcoma. Each of the 2 carcinomas, in mice 3213 and 3217, was preceded by a papilloma. In No. 3213 the papilloma appeared 5 weeks after the application, persisted for another 3 months, then began to grow deep. This animal was killed 4½ months after the application. Microscopically the tumor was a differentiated, heavily keratinized, squamous cell carcinoma.

In No. 3217 the papilloma appeared as a small warty growth 7 weeks after the application and persisted, without showing any distinct increase in size, for another 7 months, when it began to grow deep and the development of malignancy was suspected. The animal was allowed to live for another 2 months. It was killed 11 months after the application when an isolated, round, ulcerating growth about 1.25 cm. in diameter was present at the posterior end of the painted area. Enlarged lymph nodes were found in both axillae. Upon microscopic examination the tumor was found to be a highly anaplastic carcinoma showing numerous mitoses (Fig. 1). The cells varied greatly in size and shape, and keratinization was scanty. Both the lymph nodes were filled with metastatic growths having features characteristic of the primary tumor (Fig. 2).

* This investigation was aided by a grant from an anonymous donor.

The third malignant growth, in mouse 3219, was not preceded by a papilloma. It was first noticed 7 months after the application, as a tumor that appeared to have originated below the surface of the skin. It grew rapidly and the mouse was killed 1 month later, 8 months after the application. On microscopic examination it was found to be a spindle cell sarcoma. The epidermis was histologically nearly normal except for a slight hyperplasia where it covered the sarcoma.

The anaplastic carcinoma of mouse 3217 presents as an interesting feature the combination of a long period of induction with rapid growth and a high grade of malignancy as evidenced by the metastatic spread to lymph nodes. This disposes of the suggestion that carcinomas with a long period of induction grow more slowly and are less malignant than those with a very short period.

SUMMARY

It has been demonstrated for a third strain—the New Buffalo—that a single application of methylcholanthrene in benzene can induce malignant tumors. Of 12 effective mice 2 developed carcinomas and 1 a sarcoma. Of 4 different strains tested so far by a single application of a potent carcinogen only one has given a negative result. A positive carcinogenic response to a single application of a potent carcinogen is, therefore, not an exceptional phenomenon restricted to one particularly susceptible strain of mice. It is noteworthy that one of the carcinomas had a very long period of induction—9 months—and that both its morphology and its biological behavior characterized it as a very malignant type of growth.

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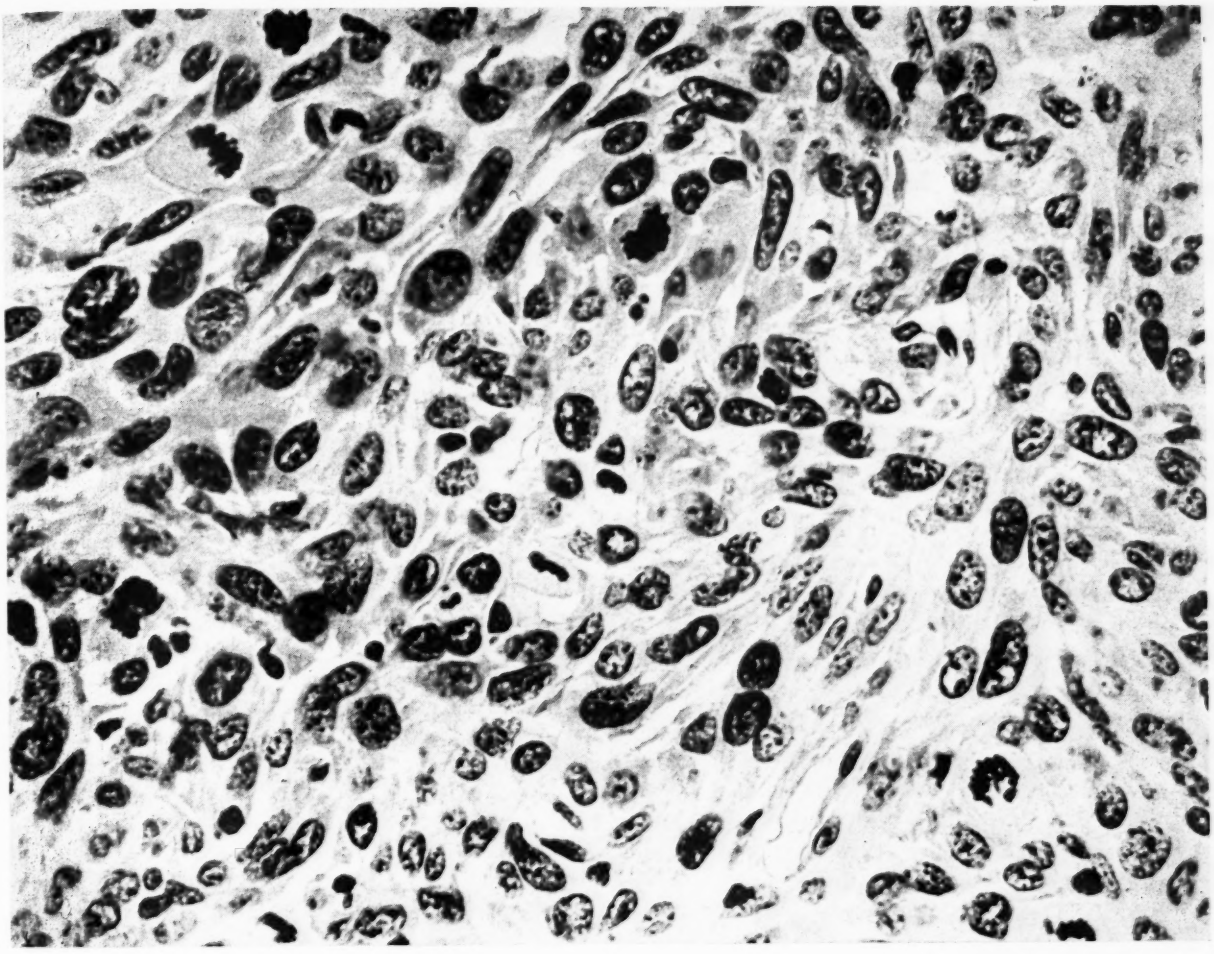

FIG. 1.—Mouse 3217. Primary skin carcinoma that developed 9 months after a single application of methylcholanthrene to the back of a New Buffalo strain mouse, showing the highly anaplastic character of the growth. At least 8 mitoses can be counted in this single high power field. Bouin fixation. Hematoxylin and eosin. Mag. × 580.

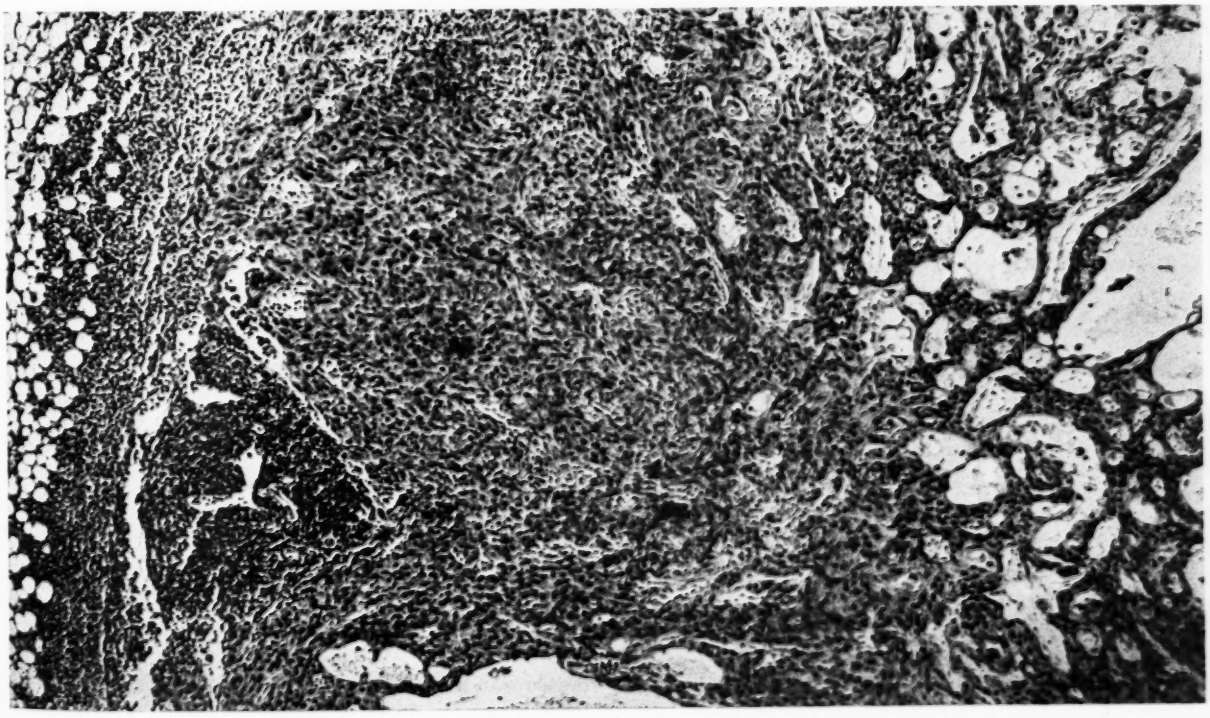

FIG. 2.—Mouse 3217. Lymph node invaded by the metastatic growth. Cells show the same features as those of the primary tumor of Fig. 1. Bouin fixation. Hematoxylin and eosin. Mag. × 90.

The Carcinogenic Activity of Some New Derivatives of Aromatic Hydrocarbons

I. Compounds Related to Chrysene*†

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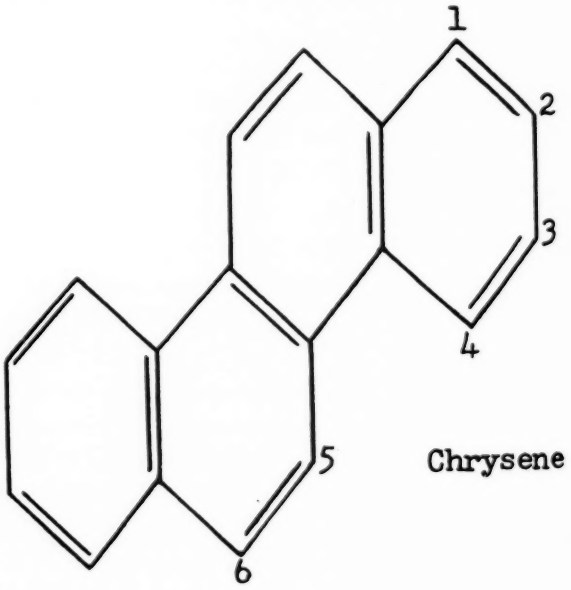
(Received for publication January 27, 1943)

The chrysene molecule contains the phenanthrene nucleus as do the natural steroids and the well known carcinogenic agents, methylcholanthrene, dibenzanthracene, and benzpyrene. However, the benzanthracene ring structure common to the carcinogenic agents is lacking in chrysene and also in the natural steroids. Chrysene is not estrogenic (2) but it is related structurally to the natural steroid hormones, and its structure invites comparison with that of diethylstilbestrol also (3, 4). If these structural relationships should find a counterpart in the biological activity of chrysene derivatives it would seem wise to test carefully the carcinogenic properties of such substances before their possible introduction into medicine or industry.

Chrysene itself has been thoroughly tested by over a dozen investigators (8, 14) and has been found almost if not entirely devoid of carcinogenic action. Pollia (13) has examined a number of commercially useful chrysene derivatives with negative results. Other derivatives that have been tested have proved carcinogenically inactive (8, 14) with two exceptions; Shear (14) obtained a single tumor in a group of 20 mice injected with 6-methylchrysene and Hewett (9) demonstrated considerable activity in 5,6-dimethylchrysene (1,2-dimethylchrysene according to the British system of numbering) by skin-painting experiments. The results obtained on injecting the latter compound subcutaneously are reported in the present paper.

A number of alkyl and alkylene derivatives of chrysene have been synthesized in recent years, including 4-methylchrysene (6), 5-methylchrysene (11, 7), 4,5-methylenechrysene (5), 4,5-dimethylchrysene (12) and 5,6-dimethylchrysene (11, 9). The ultraviolet absorption spectra have been reported by Jones (10) and by Brode and Patterson (1). We were fortunate in obtaining samples of these compounds for carcinogenic tests from Dr. Louis F. Fieser, some of them prepared in his laboratory and others synthesized by Dr. Melvin S. Newman at Ohio State University.

Carcinogenic tests were carried out according to a standardized technic on male mice 2 to 3 months old of the Swiss and C3H strains, which were obtained from the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine. The mice were fed on a diet of Purina dog chow and water supplemented with cod liver oil. The compounds were dissolved in tricaprylin and 0.2 cc. of the solution, containing 1 to 4 mgm. of the compound, was injected in a single dose under the skin of the rump. The mice were then examined weekly for tumors. The date of appearance of a tumor was taken as the day on which an easily palpable nodule appeared at the site of the injection, provided the nodule showed progressive growth thereafter and proved to be a sarcoma on subsequent histological examination. Transplants were attempted from tumors arising in mice injected with four of the five compounds and were successful in all cases.



Chrysene

* This investigation was aided by a grant from The Jane Coffin Childs Memorial Fund for Medical Research.

† The compounds used in these experiments were selected and synthesized in part by Professor L. F. Fieser and his associates, of the Department of Chemistry, Harvard University, and in part by Dr. Melvin S. Newman, of Ohio State University.

The results of the carcinogenic tests are presented in Table I. It is apparent that each of the compounds has yielded one or more sarcomas at the site of injection but that only 5-methylchrysene has shown a high degree of activity. The speed of tumor induction by this compound shows its activity to lie intermediate between that of 20-methylcholanthrene and 1,2,5,6-dibenzanthracene as tested by the same technic.

The occurrence of only a single tumor at the site of injection in a group of test mice is doubtful evidence of the carcinogenic activity of a compound. Tumors occurring at a distance from the site of injection may have some significance but it is difficult to evaluate. Therefore, our results have given evidence of only weak or questionable activity in the case of 4-methylchrysene and 4,5-dimethylchrysene. The other compounds may safely be considered carcinogenic for mice.

TABLE I: CARCINOGENIC ACTIVITY OF CHRYSENE DERIVATIVES

Compound	Date of injection	Number of mice	Strain	Dose, mgm.	Effective total *	Tumors at site of injection	Induction time of earliest tumor, days	Average induction time, days	Transplants	
4-Methylchrysene	Sept. 19, 1939	5	C3H	4	4	0	—	—	—	1 epidermoid carcinoma of epididymis. 1 sarcoma of scrotum
	Sept. 19, 1939	5	Swiss	4	5	0	—	—	—	
	Jan. 14, 1941	20	C3H	2	17	1	170	170	+	
5-Methylchrysene (Newman)	Jan. 9, 1940	20	Swiss	2	4	0	—	—	—	3 adenomas of lung. 1 papilloma of esophagus. 1 leukemia
	Jan. 7, 1941	10	C3H	2	9	7	114	136	+	
	June 24, 1941	10	C3H	2	9	3	79	125	—	
4,5-Methylenechrysene	Dec. 10, 1940	20	C3H	2	18	4	163	235	+	
4,5-Dimethylchrysene (Newman)	Jan. 25, 1940	20	Swiss	1	12	0	—	—	—	4 adenomas of the lung
	Apr. 22, 1940	15	Swiss	2	3	1	571	571	—	
	July 1, 1941	10	C3H	2	4	0	—	—	—	
5,6-Dimethylchrysene † (Newman)	Jan. 25, 1940	15	Swiss	2	9	0	—	—	—	2 adenomas of the lung
	Dec. 31, 1940	10	C3H	2	9	2	155	163	+	

* The "Effective total" is the number of mice alive at the time the first tumor appeared.
In those groups in which no tumors appeared, the number of mice alive 6 months after injection is used.
† Previously tested by Hewett (9) and found active.

SUMMARY

Tests of the carcinogenic action of five derivatives of chrysene are reported. 5-Methylchrysene showed a high degree of activity; 4,5-methylenechrysene and 5,6-dimethylchrysene were moderately active, and 4-methylchrysene and 4,5-dimethylchrysene weakly or questionably so.

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On the Reported Production of Tumors by Normal Liver Cells of Mice Bearing Tumors Produced by Methylcholanthrene*

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Selle, Brindley, and Spies (4) have reported the induction of tumors in mice by the transplantation of liver cells from mice bearing sarcomas induced by methylcholanthrene. The tumors arising at the site of the injected liver cells were similar in their histological structure to the induced tumors of the hosts. Selle and his associates noticed also that they were able to produce tumors with liver cells of C3H mice in those of the same strain, but not in C57 black mice, nor did tumors appear after the injection of C3H and C57 mice with liver cells originating from mice of the C57 strain bearing methylcholanthrene-induced tumors, or with liver cells of normal C3H mice.

EXPERIMENTS

The Strong A, C3H, RIII, and Bagg high cancer strains; C57 and S low cancer strains; and C57 × RIII low cancer strain hybrids were used in the present experiments.

In view of the findings of Selle and his collaborators, who produced tumors with liver cells from C3H mice, a strain of high incidence, mice of this strain and of the high cancer strains Strong A and RIII, as well as of the medium cancer strain Bagg, were used as donors of livers. Mice of both high and low cancer strains served as recipients.

Mice of Strong A, C3H, RIII, and the Bagg strains were inoculated with 0.25 cc. of a 0.5 per cent solution of methylcholanthrene in lard.[1] After the induced tumors had reached 1 to 2 cm. in diameter, livers were removed aseptically from the bearers. Part of each liver was kept for histological examination and the rest ground in a sterile mortar, three times the amount of saline being added slowly until a uniform suspension was obtained. Three-tenths cubic centimeter of the liver suspension was injected subcutaneously into each mouse.

TABLE I

Group	Source of liver	Mice injected	Number of mice
I	BAGG No. 27	RIII(3 + 3), BAGG(3 + 3), C57 × RIII(3 + 3), C57(3 + 3)	24
II	RIII No. 12	RIII(1 + 5), STRONG A(0 + 4), S(3 + 3)	16
III	RIII No. 19	RIII(0 + 6), S(0 + 5), C57 × RIII(0 + 6)	18
IV	RIII No. 15	RIII(9 + 0), S(4 + 4)	17
V	C3H No. 1	RIII(2 + 6), C3H(7 + 1)	16
VI	STRONG A No. 6	RIII(3 + 7), S(7 + 1), STRONG A (4 + 4)	26
VII	RIII No. 11	RIII(3 + 3), C57(3 + 3), C57 × RIII(3 + 3)	18

Figures in parentheses indicate numbers of mice injected. The first figure in each case denotes females, the second denotes males.

The tumors in C3H mice that were induced by liver cells of C3H mice with methylcholanthrene tumors developed in both males and females, in young and old mice, and in the comparatively short time of 3 to 6 weeks. Microscopic examination of the livers with which tumors were produced did not show any pathological changes in the liver cells.

In view of the importance of these results, and since Steiner (5); Kleinenberg, Neufach, and Shabad (3); Hieger (2); and des Ligneris (1) have all reported the production of tumors in mice with liver extracts from human beings with cancer of other organs, it was decided to repeat the experiments of Selle and his collaborators with several different inbred strains of mice.

Seven groups altogether, comprising a total of 135 mice, were used. The mice were of different ages, several weeks or months old, and approximately half (66) were females, the rest (69) males (Table I).

The average time of observation lasted 10 weeks.

* Because of the difficulties of international communication the author has not read proof of this article.

[1] The methylcholanthrene was kindly supplied by Professor E. L. Kennaway.

No tumors were observed in any of the injected mice even after a period extending to 4 months. Histological examination of the injected liver cells did not show any pathological changes.

The failure to elicit sarcomas in C3H mice with livers from the same strain was to have been expected, for Selle and his group had positive results with only about one liver out of nine. The remainder of this experiment brings out once more the strain differences suggested in their report.

SUMMARY

Mice of the Strong A, C3H, RIII, and Bagg high cancer strains; S and C57 low cancer strains; and C57 × RIII low cancer strain hybrids were injected with liver suspension from mice belonging to RIII, C3H, Strong A, and Bagg strains bearing sarcomas induced by methylcholanthrene.

No tumors were produced in this way during a period of several months.

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The Effect of Temperature upon Ultraviolet Carcinogenesis with Wave Lengths 2,800–3,400 Å*

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INTRODUCTION

Since the discovery of the carcinogenicity of ultraviolet radiation, work on this subject has been directed toward specification of the wave lengths involved and determination of the energy requirements of the process (1, 2, 3, 8). A filter for the isolation of wave lengths 2,800–3,400 Å was described and the production of tumors with this portion of the spectrum reported in a previous publication from this laboratory (1). However, the efficiency of carcinogenesis was not so great as when the whole spectrum of the mercury arc was used, and there seemed to be some other factor or factors that affected carcinogenesis. The present report deals with the investigation of one of these factors, namely, temperature.

One difference in the irradiation of mice with filtered as compared to unfiltered radiation was that in the latter treatment more heat energy was received by the animals. Heat is known to increase the effect of roentgen irradiation on the skin of young rats (4, 5) and presumably the response to ultraviolet irradiation might likewise depend upon the temperature. Moreover, it has been shown that high environmental temperatures (92° F.) increase the rate of development of subcutaneous methylcholanthrene tumors and of transplantable methylcholanthrene tumors (10).

EXPERIMENTAL

Young adult white ABC mice of both sexes were used. They were kept on shavings in ordinary metal box cages with Purina dog chow and water available at all times except during the irradiation. At this time they were transferred to a special cage 25.5 cm. square by 3 cm. deep, constructed of wire mesh, and divided into 24 individual compartments to prevent the mice huddling together and to minimize movements (8).

Groups of mice were irradiated at room temperature, at a relatively high, or at a relatively low temperature. One group was placed in a thermostatically controlled oven at 35–38° C. during irradiation. It was necessary to equip the oven with forced ventilation to control the humidity and to insure survival of the mice. Another group was placed in an insulated, ice-cooled box at approximately 3–5° C. while being irradiated. A control group was irradiated at room temperature in the usual manner (1). In the first two cases the mice were subjected to the irradiation temperatures for a 30 minute equilibration period before the irradiation was begun. Evans, Goodrich, and Slaughter (5) have reported that the rectal temperature rapidly approaches that of the skin at low and high temperatures. It is likely, however, that with our method of cooling the body temperature of the mice did not fall more than a few degrees.

In all cases the mice were irradiated 30 minutes a day, 6 days a week, with the light of a medium pressure mercury vapor lamp [1] passed through a filter previously described (1), which isolated the wave lengths 2,800–3,400 Å. The energy incident upon the irradiation cage was measured with a multiple junction copper-constantan thermopile in conjunction with a high sensitivity galvanometer (1). All groups received an intensity of approximately 4,200 ergs/cm.^{2}/sec. resulting in a daily dose of about 0.75×10^7 ergs/cm.^{2}

RESULTS AND DISCUSSION

The specific data on intensity and dose are given in Table I, together with the number of days at which a 50 per cent tumor incidence (1) was developed in each group. These results are compared in Fig. 1 with data previously obtained (1). Curve A represents the rate of tumor development at room temperature due to wave lengths 2,800–3,400 Å exclusively. It will be seen that point 1 for the mice irradiated at 3–5° C. lies close to curve A. On the other hand, point 2 for the mice irradiated at 35–38° C. lies well below curve A.

* This investigation was aided by a grant from the Jonathan Bowman Fund for Cancer Research.

** Finney-Howell Cancer Research Fellow.

[1] Manufactured by the Burdick Corporation, Milton, Wisconsin.

The difference between the results obtained by irradiation at room temperature (23° C.) and at 35–38° C. is definite, the efficiency being significantly increased at the higher temperature. The data show, however, that there is little if any difference between irradiation at 3–5° C. and at room temperature, and that only at the highest level of 35–38° C. does the external temperature give an effect. Whether this variation is the result of a more efficient compensation by the mouse for the low temperature, or a real effect, remains an undecided point. The results obtained at 35–38° C. may not, of course, represent a direct effect upon the carcinogenic process. It has been shown that mineral oil applied to the surface of the ears just prior to treatment with unfiltered (7) or filtered (9) radiation accelerates the rate of carcinogenesis, probably by filling in crevices in the skin, thus cutting down reflection and refraction losses and giving a higher effective transmission. The heat may have caused sweating of the mice and possibly increased, in the same manner as mineral oil, the transmission of ultraviolet radiation to the subdermal layers of the skin. However, gross inspection of the animals during irradiation showed that only during humid weather were the ears appreciably moist. Furthermore, one group, which was irradiated during the summer months when humidity was high, gave results that were not significantly different from those obtained in a group irradiated in late fall and early winter when humidity was low. Another point to consider is that the elevated temperature may have acted by giving a better circulation to the skin and a consequent quickening in the metabolism of the affected cells. Since the mice were kept at the elevated temperature only during irradiation, this indirect effect does not seem so probable because of the short time of increased blood supply. It appears more likely that the increased efficiency represents a direct thermoacceleration on the immediate reaction initiated by the ultraviolet radiation. In any event the results would seem to indicate that one of the reasons for the different efficiencies of the two procedures, filter and nonfilter, may be the effect of the heat present in the latter case. It would be interesting to determine what effect temperature would have on ultraviolet carcinogenesis if the animals were kept in cold or warm environments continuously, as in the experiments of Wallace, Wallace, and Mills (10), instead of only during the irradiation period.

TABLE I: EFFECT OF TEMPERATURE UPON ULTRAVIOLET CARCINOGENESIS WITH 2,800-3,400 Å

Procedure	Effective total *	Daily dose, ergs/cm.²	Time to 50% tumors, days	Total dose, ergs/cm.²
Irradiated, 3–5° C.	18	0.72×10^7	252	156×10^7
Irradiated, room temperature	21	0.76	237	152
Irradiated, 35–38° C.	33	0.74	186	125

* Number of mice surviving at time of appearance of first tumor.

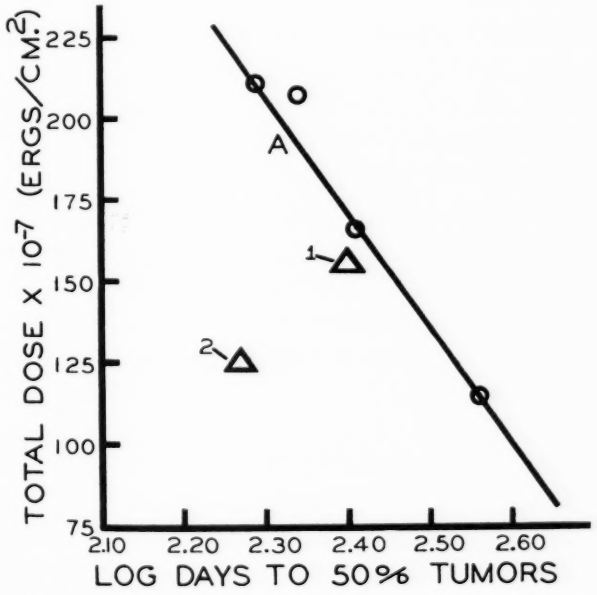

FIG. 1.—Curve A plotted from data obtained with wave lengths 2,800–3,400 Å at room temperature. Point 1, effect of irradiating with 2,800–3,400 Å at 3–5° C. Point 2, effect of irradiating with 2,800–3,400 Å at 35–38° C.

The present study, when considered with previous work (1, 8), suggests that the carcinogenic process as initiated by ultraviolet light may be modified by other factors. Heat affects the process and there is some evidence that wave lengths, *e. g.*, 3,650 Å, other than those absolutely essential are effective in speeding up carcinogenesis (9). Apparently a reaction takes place whose initiation requires the absorption of specific wave lengths, but whose continuation rate may be modified by energy gained from other sources such as heat.

SUMMARY

The effect of temperature on ultraviolet carcinogenesis with wave lengths 2,800–3,400 Å was investigated, and it was found that the production of tumors was more efficient at 35–38° C. than at room temperature. There was little difference, however, in the rate of carcinogenesis at 3-5° C. and at room temperature.

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Growth and Regression of Frog Kidney Carcinoma Transplanted into the Tails of Permanent and Normal Tadpoles*

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In an earlier paper (1) it was shown that the kidney carcinoma (3) of the adult frog, *Rana pipiens,* grew and maintained its characteristic structure when transplanted to various sites in young tadpoles. There was no evidence in these experiments that the early larval environment exerted any morphogenetic or growth-controlling effects on the carcinoma. Older larvae approaching metamorphosis did, however, have a pronounced effect on the tumor such that well established implants quite uniformly underwent regression. Observations of implants in the dorsal mesenchyme of the tail were the most complete. In this site the carcinoma grew very well in young larvae (20 mm. → 50 mm.), but regressed rapidly and uniformly in premetamorphic stages of development (50 mm. → 65 mm.). This regression was initiated before metamorphic absorption of the tail had begun, and appeared not to be caused by lack of space for growth, or by loss of vascular supply. We thought that some undetected change in the host tail, associated with metamorphosis but preceding it, might be responsible for the tumor regressions. To test this possibility we have, in the present work, compared the behavior of carcinoma implants in the tails of normal tadpoles with the behavior of implants in the tails of tadpoles rendered incapable of metamorphosis by removal of thyroid or pituitary.

METHODS

Host tadpoles were obtained from fertilized eggs produced in the laboratory by the usual pituitary injection technic. After fertilization the eggs were divided into four groups, and each group was reared under conditions previously described (1). When the embryos were in early tailbud stage (stages 17 to 18) (4) the pituitary anlagen were excised from one set of animals. Later on when the embryos were in the 6 to 7 mm. stage (stages 20 to 21) the rudimentary thyroids were removed from a second set of embryos. The remaining two groups of embryos developed normally as controls for the thyroidectomized and hypophysectomized animals.

When the tadpole stage was reached all animals were fed a diet consisting of: (a) lettuce cooked for 10 minutes under 15 pounds' pressure, and (b) a dried food made up of a mixture of 37 gm. of pablum, 37 gm. of finely grated boiled liver, and 250 cc. of milk. Tadpoles were reared in squat, half-gallon fish bowls, 10 to a bowl, until they were 16 to 25 mm. in total length.[1] At this time animals of uniform size were selected from each group to receive the carcinoma implants. Amongst the controls the only factor to be considered in this selection was the size, or total length. The majority of the hypophysectomized animals, about 75 per cent, had the silvery appearance indicating that the gland had been removed. These silvery animals were selected as hosts. Thyroidectomized tadpoles during early larval stages are indistinguishable from normal animals. In this group selection had to be made on the basis of total length alone. The control tadpoles metamorphosed usually

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[1] Note on the mean total lengths of tadpole hosts at the beginning of these experiments:

Experiments 1 and 2:	
Hypophysectomized hosts	16.0 mm.
Thyroidectomized and control hosts	17.0 to 18.5 mm.
Experiment 3:	
Hypophysectomized hosts	17.0 mm.
Other hosts	20.0 to 21.5 mm.
Experiment 4:	
Hypophysectomized hosts	23.5 mm.
Other hosts	25.0 to 25.5 mm.

The extreme individual measurements fell within ± 3 mm. of the mean values given above except in experiment 4 where the extremes were ± 5 mm. from the means.

within 70 to 100 days following the beginning of the experiment; *i.e.,* following the time of implantation when the tadpoles were 16 to 25 mm. in total length. Of the experimental animals one hypophysectomized and one thyroidectomized tadpole metamorphosed normally, showing that in these 2 cases the glands had not been completely removed. The remaining experimental tadpoles, 43 hypophysectomized and 48 thyroidectomized, were autopsied at times ranging from 140 to 205 days following the beginning of the experiment. None of these animals showed any signs of metamorphosis and were thus quite certainly completely without anterior pituitary or thyroid tissue.

camera lucida drawings as an index of the size of the implant. The width could be measured only approximately because the fin lying above the implant interfered with the dorsal view of it. However, these rough measurements showed that implant width changed proportionately with length and height.

Organization of experiments.—This investigation consisted of four experiments (Table I). In each experiment carcinoma from a single donor frog was implanted into the tails of permanent and normal tadpoles derived from one clutch of eggs. Thus within each experiment variations in heredity were, of course, nil in the donor, and reduced to the lowest

TABLE I: THE NUMBERS OF THYROIDECTOMIZED, HYPOPHYSECTOMIZED, AND CONTROL TADPOLE HOSTS IN EACH OF THE FOUR EXPERIMENTS REPORTED IN THIS PAPER

In each experiment carcinoma from a single adult frog was implanted into the tails of tadpoles derived from a single clutch of eggs. The numbers of animals that died, were lost accidentally, or that lost their implants are given for the experimental period covered in this report; *i.e.,* the period during which the carcinoma implants grew and regressed.

	Thyroidectomized hosts				Hypophysectomized hosts				Controls				
Experiment No.	Total number	Tadpoles lost	Implants lost	Effective total	Total	Deaths	Implants lost	Effective total	Total	Deaths	Tadpoles lost	Implants lost	Effective total
1	12	0	0	12	10	0	0	10	22	0	0	0	22
2	15	0	1	14	10	1	1	8	26	0	1	1	24
3	10	0	1	9	12	0	1	11	22	0	0	1	21
4	12	2	2	8	12	0	5	7	24	1	0	5	18
Totals....	49	2	4	43	44	1	7	36	94	1	1	7	85

TABLE II: THE PROPORTION OF THE EFFECTIVE TOTAL OF CARCINOMA IMPLANTS THAT TOOK AND THE PROPORTION THAT REGRESSED AFTER GROWTH IN THE TAILS OF PERMANENT AND NORMAL CONTROL TADPOLES

Hosts	Effective total number of implants (one per host)	Number of takes	Takes, per cent	Number regressed	Regressed, per cent
Thyroidectomized	43	23	54	23	100
Control	43	24	56	23	96
Hypophysectomized	36	19	53	18	95
Control	42	25	60	25	100

Donor tumors were detected in adult frogs by palpation. Healthy, growing parts of the tumors were first minced with scissors in cold sterile Ringer's solution and then implanted into the dorsal mesenchyme of the anterior third of the tadpole tails according to the technic previously described (1).

Following implantation tadpole hosts were reared singly in finger bowls and observed in the gross every day. Implants were examined under the dissecting microscope once a week, and camera lucida outline drawings of lateral views of the implants were made every 1 to 2 weeks. The hosts were reared for 4½ to 6½ months, at which times all surviving animals were killed with the anesthetic, MS-222, and autopsied under the dissecting microscope.

In analyzing the results we used the mean of the two principal dimensions (length and height) of the

practicable level amongst the hosts. Actually, on analyzing our results we found no significant differences in the behavior of the implants in the different experiments, and most of the data are presented in subsequent parts of this report in summary form.

The number of hosts that died or were lost by accident, or that lost their implants, were subtracted from the total number of hosts (Table I) to give the effective totals upon which calculations of percentage takes and percentage regressions were based (Table II).

RESULTS

General.—The general behavior of tail implants in all tadpole hosts in this investigation was the same as that previously described (1) and will be summarized only briefly here. For a variable period fol-

lowing implantation, usually 2 to 3 weeks, the carcinoma implants remained approximately constant in size. At the end of this latent period successful implants began to grow. From microscopic observations in living animals and from sectioned material it appeared that from the beginning of growth the tumor took the form of tubules, or cysts filled with papillary extensions of the cyst wall. This type of growth is characteristic also of the carcinoma in the adult frog kidney. It continued in the tadpole hosts for about 4 weeks. Implants studied at regular intervals during the growth period were found to be well circumscribed and composed entirely of carcinoma. While they were small they had a semitranslucent whitish appearance; as they grew larger they acquired an opaque ivory-white color. The implant surface was shiny and very sharply marked off from the surrounding mesenchyme. It remained uneven throughout the growth period owing to the extension outward of growing cysts and tubules.

At the end of the implant growth period both the normal controls and the thyroidectomized tadpoles were approximately 54 mm. in average total length; hypophysectomized hosts were considerably smaller, 42 mm. average total length. At this time implants in both normal and permanent tadpoles ceased growth and began to regress rapidly. During regression the implants acquired a yellowish-white color and fuzzy outlines that made them appear to merge peripherally with surrounding mesenchyme. Decrease in size went on steadily until the implants themselves disappeared entirely, leaving only small masses of dense mesenchyme at the sites they had occupied. The histological changes accompanying this regression have been described previously (1).

The processes of growth and regression recapitulated above occurred in the same manner in normal and in permanent tadpoles. Thus the thyroid and pituitary glands and the metamorphic processes with which they are involved have no influence on the qualitative aspects of carcinoma growth in the tadpole tail. A more detailed quantitative analysis is given in the following sections of this report.

Quantitative aspects of the behavior of carcinoma implants in the tails of permanent and normal tadpoles.—Hypophysectomy and thyroidectomy of tadpole hosts conceivably could influence the percentage of implants that succeed in taking and growing, the rate of growth, the maximum size attained, the percentage that regress after growth, and the rate of regression. All these aspects of the behavior of carcinoma implants have been analyzed.

Table II lists the data on the proportion of the effective total of implants that took and the proportion that regressed after growth. Implants were listed as takes when they assumed the typical appearance of growing carcinoma and showed a definite increase in size. In some cases the apparent size increased owing to the development of a diffuse condition in the implant preceding resorption. These cases were not entered as takes. Implants were listed as regressing when they assumed the characteristic appearance of regressing carcinoma and underwent progressive decrease in size.

TABLE III: INITIAL DIAMETER, MAXIMUM DIAMETER, RATE OF GROWTH, AND RATE OF REGRESSION OF CARCINOMA IMPLANTS IN THE TAILS OF PERMANENT AND NORMAL CONTROL TADPOLES. THE VALUES LISTED REPRESENT MEANS AND THEIR STANDARD ERRORS IN ALL CASES

Hosts	N_g	d Initial diameter, mm.	D Maximum diameter, mm.	T Time, days	Growth rate, mm./day $\times 10^3$	N_r	Regression rate, mm./day $\times 10^3$
Thy	23	0.41 ± 0.015	0.79 ± 0.04	43 ± 3.1	8.8 ± 0.5	13	23.4 ± 2.4
Cont.	23	0.41 ± 0.015	0.81 ± 0.05	44 ± 3.1	9.1 ± 0.8	14	17.4 ± 2.5
Pit	18	0.37 ± 0.004	0.75 ± 0.03	45 ± 4.5	10.0 ± 1.3	18	21.4 ± 2.1
Cont.	25	0.41 ± 0.003	0.90 ± 0.08	46 ± 3.1	10.9 ± 1.6	18	20.3 ± 3.0

T = Time required for growth of implants from minimum to maximum diameter.
N_g and N_r = Numbers of implants employed in calculations of growth rates and regression rates respectively.
For additional explanation see text.

An inspection of Table II shows that the proportion of the effective total of implants that took varied from 53 to 60 per cent in the various groups of hosts. The differences between normal and permanent tadpoles are most probably not significant. There are also no significant differences in the proportion of implants regressing in the different groups of hosts. In every group all, or practically all, the established implants regressed during later larval development of the host. From these data we conclude that the permanent and normal tadpoles we used provided equally satisfactory conditions for the initiation of carcinoma implant growth. They were also equal in their capacity to initiate regression, or in their inability to support continued growth, during later larval stages.

Table III lists maximum sizes attained by the implants, and their growth and regression rates. The over-all growth rate for each implant was calculated

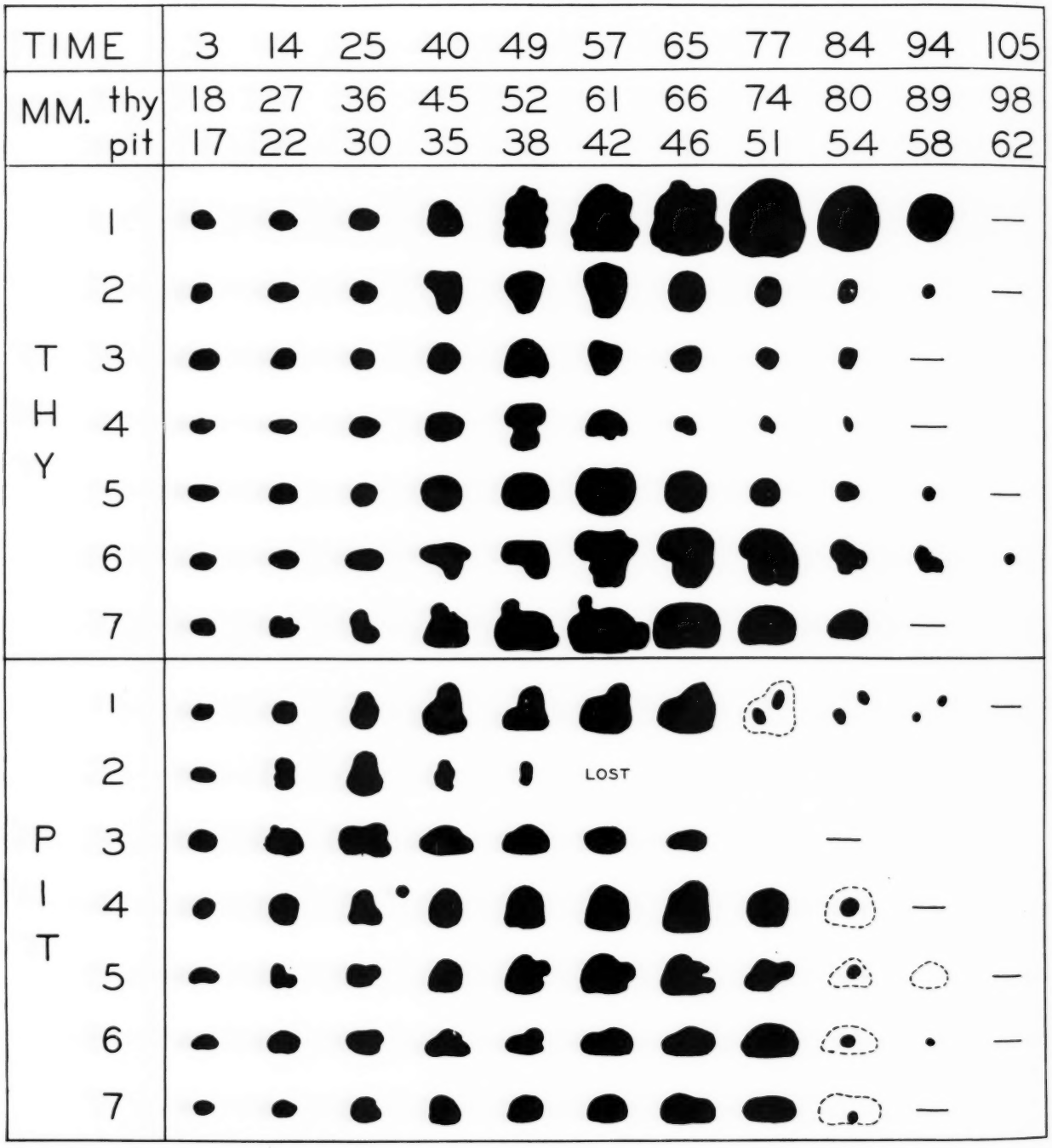


FIG. 1.—Growth and regression of carcinoma implants in the dorsal mesenchyme of the tails of permanent tadpoles (experiment 1). The blacked-in camera lucida outline drawings represent the lateral view of the implants in all cases. Compare with Fig. 2.

Definitions: Time = Elapsed time in days following implantation of the tumor into the tail. Mm. = Total length of the host tadpoles in millimeters. Thy = Thyroidectomized host tadpoles. Pit = hypophysectomized host tadpoles. Mag. × 8.2 for all drawings.

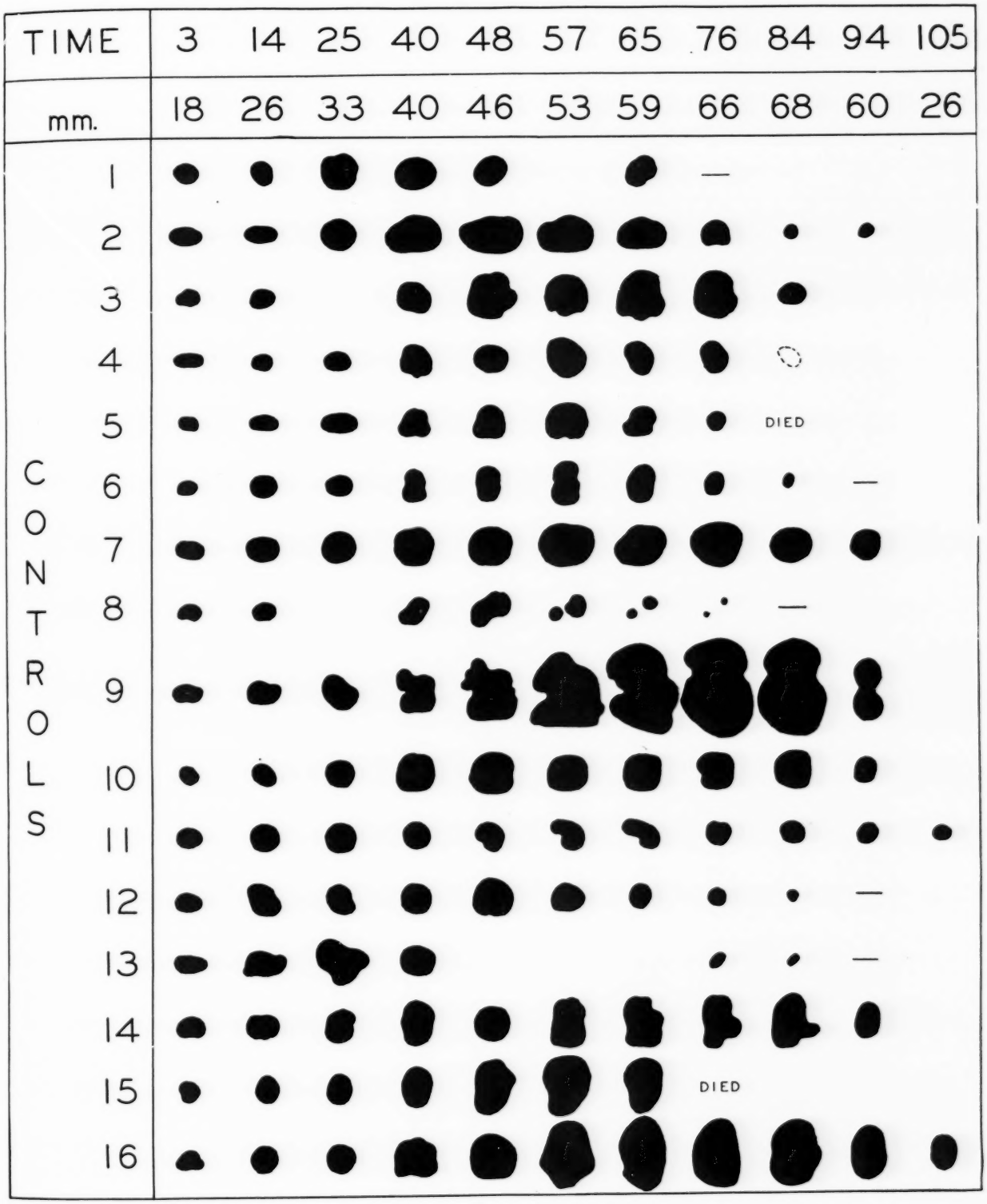
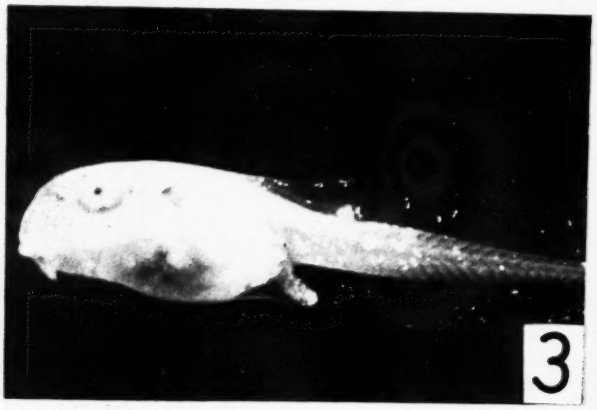
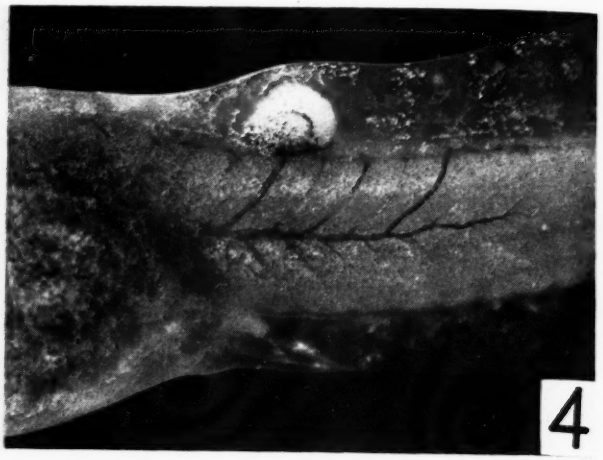
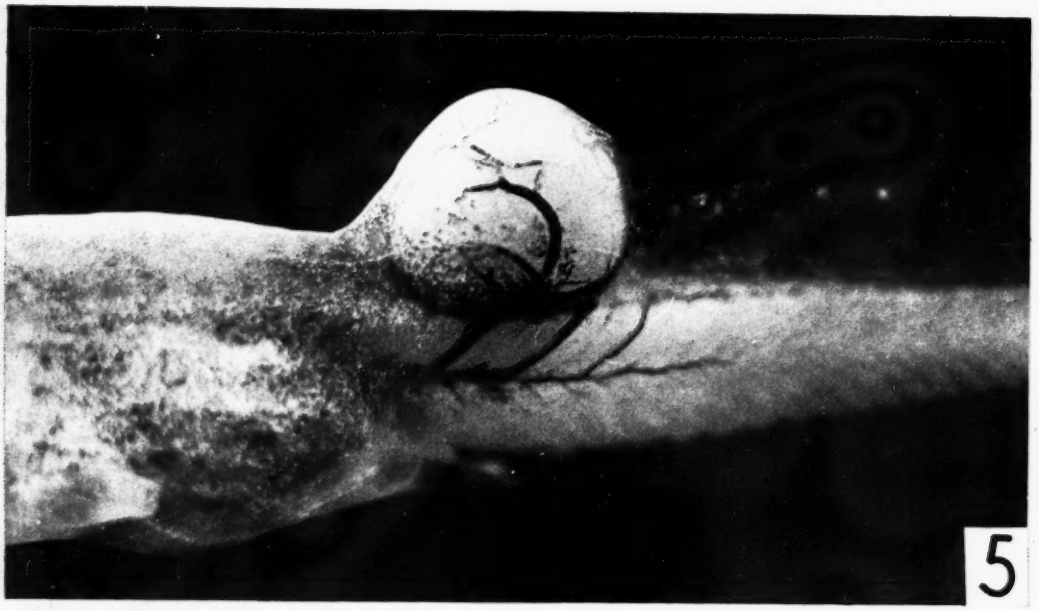
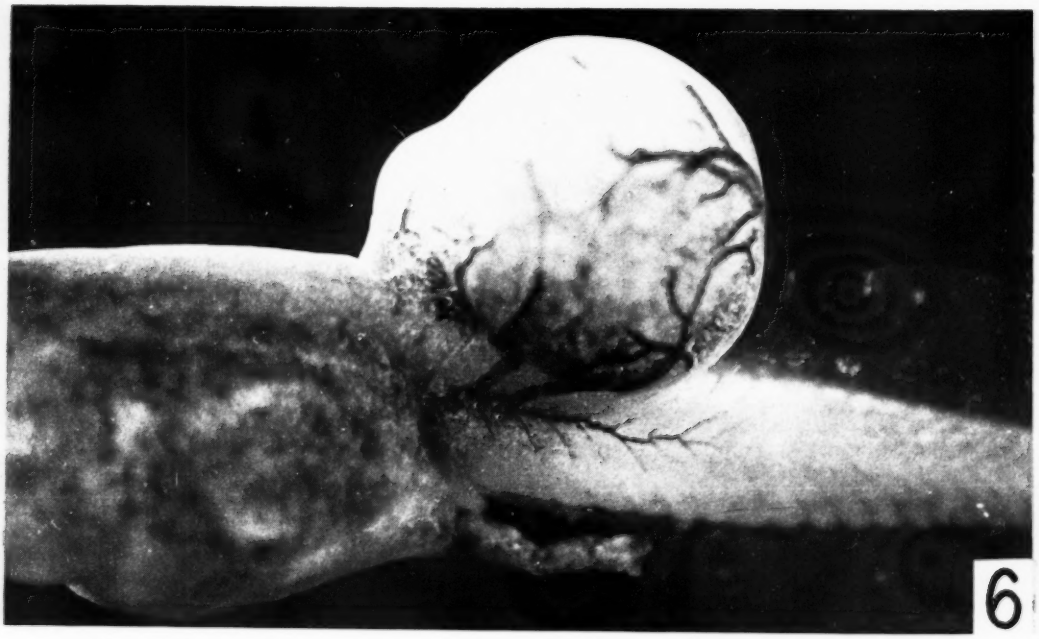


FIG. 2.—Growth and regression of carcinoma implants in the dorsal mesenchyme of the tails of normal tadpoles (experiment 1, controls). Many hosts metamorphosed before implants had regressed completely. In these cases regression was found to be complete at the time of autopsy 6½ months after implantation. In all cases lateral views of the implants are represented. Definitions of abbreviations as for Fig. 1. Mag. × 8.2.









FIGS. 3–6

by dividing the maximum increase in diameter (maximum diameter minus original diameter) by the time in days required for this amount of growth to take place. The mean growth rate and its standard error were calculated for each group of hosts as listed in Table III. The regression rates were calculated in the same way, subject to the following conditions in obtaining the original data. The regression of implants in many normal tadpoles was not complete at the time of metamorphosis when the remnants of implants were drawn into a position adjacent to the posterior tip of the urostyle. In this position the implants could not be observed further in the living animal because of the opacity of the overlying skin. In such cases the difference between the maximum diameter and the last diameter measured preceding metamorphosis was divided by the corresponding time interval to give the regression rate. That these tumors subsequently underwent complete regression was determined at autopsy several weeks after metamorphosis. It should also be noted that the regression rates for some implants could not be determined accurately, mainly because the tumor tissue merged with the surrounding mesenchyme and the exact limits of the implant could not be measured. Cases of this nature were eliminated from the calculations, which accounts for N_r being smaller than N_g in Table III.

These data, summarized in Table III and illustrated in Figs. 1 and 2, show that the maximum sizes attained and the rates of growth and regression of carcinoma implants were not significantly different in normal and in permanent tadpoles. Thus there appears to be no demonstrable effect, quantitative or qualitative, of hypophysectomy, thyroidectomy, and metamorphic changes in the host on the growth and regression of kidney carcinoma in tadpole tails.

Special cases.—Two exceptional and important cases were left out of the general description of the results given above. In two hosts, one hypophysectomized and one a normal control tadpole, the carcinoma implants failed to regress at the usual time and grew to relatively large sizes. These cases may be of sufficient interest to be described briefly.

The hypophysectomized host in question ($3pit_9$) received an implant 0.25 mm. in diameter, 0.008 mm.^{3} in volume, when it was 17 mm. in total length. After a latent period of about 19 days rapid growth began. In another 26 days, at the end of the average growth period for other implants in this series, there was no sign of regression of the implant in host $3pit_9$. Rapid growth continued for an additional 41 days when the host died. At this time the total length of the host was 58 mm. and its body length, anus to snout tip, 22 mm. The implant in its tail had grown to 12 mm. in diameter with a volume, calculated on the basis of a spherical shape, of 905 mm.^{3} Thus the original implant had increased approximately 110,000 times in mass. Figs. 4, 5, and 6 are photographs of this animal taken at intervals during the growth of the tumor.

Had this been the only case of continued growth without regression some significance might have been attached to the fact that it occurred in a permanent (hypophysectomized) tadpole. However, the second case of progressive growth without regression occurred in a normal control tadpole. This animal ($3cont_{10}$) received an implant 0.5 mm. in diameter, vol. = 0.066 mm.^{3} when it was 22 mm. in total length. Growth of the implant continued throughout the larval life of the host and beyond the time when implants in other control hosts had begun to regress. During metamorphosis the implant, now 1.1 mm. in diameter, was drawn into a position in the subcutaneous tissue adjacent to the posterior end of the urostyle. No change in size or appearance was observed in the implant while the surrounding tail tissue was being absorbed. Following the completion of metamorphosis at 63 days after implantation the implant could not be seen owing to the opacity of the overlying skin. The young frog was fed with fresh liver and living *Enchytraeus* for an additional 75 days following metamorphosis, at which time death occurred. At autopsy the implanted tumor was found adjacent to the posterior end of the urostyle. It was 3.04 mm. in diameter, spherical in shape, and ivory-white in color. Its volume was calculated to be 14.7 mm.^{3} Sections showed that it had the characteristic adenocarcinoma structure.

Other observations were made on the fate of implants in control hosts during metamorphosis. These

DESCRIPTION OF FIGURES 3 TO 6

FIG. 3.—Hypophysectomized host ($1pit_1$) illustrating appearance of carcinoma implant 6 days after it had been placed in the tail. Mean diameter of implant = 0.42 mm. Host = 18 mm. in total length. Mag. × 5.1.

Figs. 4, 5, 6. Hypophysectomized host ($3pit_9$) showing unusually vigorous growth of carcinoma implant in the tail. See text for description. All mag. × 4.4.

FIG. 4.—Carcinoma implant 45 days after it had been placed in the tail. Original implant was 0.25 mm. in diameter. Diameter at 45 days = 2.4 mm. Host = 51 mm. in total length.

FIG. 5.—The same implant at 60 days. Diameter = 7.1 mm. Host = 55 mm. in total length.

FIG. 6.—The same implant at 72 days. Diameter = 9.3 mm. Host = 56 mm. in total length.

implants were in various stages of regression, but we never observed any acceleration of regression rate during the metamorphic absorption of the host tail. Judging from these latter observations, and from the behavior of the nonregressing implant described above, it appears that the factors bringing about metamorphic absorption of the tail tissues have no influence on the carcinoma implants in the tail.

DISCUSSION

The experiments described in this paper confirm results previously reported (1) in demonstrating that implants of adult frog carcinoma placed in the tails of normal tadpoles grow well in young larvae and regress in older larvae prior to metamorphosis. This paper shows in addition that carcinoma implants behave in identical fashion in the tails of nonmetamorphosing, thyroidectomized and hypophysectomized, tadpoles. Therefore changes in the host associated with metamorphosis are not responsible for tumor regression in older tadpoles unless such premetamorphic changes are independent of thyroid and pituitary secretions.

These results leave open the question of what is responsible for implant regressions in the older larvae. An earlier paper referred to above showed that as normal tadpoles approached metamorphosis the carcinoma implants became surrounded usually by densely packed spindle-shaped mesenchyme cells, and occasionally by numerous small round cells. According to the present experiments the same processes appear to take place at the same chronological age in permanent tadpoles. These accumulations of host cells are associated with the regression of the implant, and probably are an expression of the development of tissue specificity during later stages of larval development. Recently Harris (2) has shown that the same type of cellular reactions occur about homologous grafts of gastrula tissues in old *Hyla regilla* tadpoles, while no cellular responses are elicited by identical grafts in young tadpoles. In our experiments the absence of cellular reactions could account for the success of carcinoma implants in young hosts, and their appearance in old tadpoles could be responsible for the almost uniform regression of implants during the later larval life of the host.

The basis for the development of tissue specificity is unknown. Harris suggests that it may be an expression of relative lack of biochemical differentiation in early larvae, and its appearance in later stages. The present work indicates that whatever the basis of the responses may be, they are effective against cancerous as well as normal tissues, and are developed in the absence of thyroid or pituitary, and of the metamorphic alterations with which these glands are associated.

SUMMARY

Kidney carcinoma from adult frogs (*Rana pipiens*), transplanted into the dorsal mesenchyme of the anterior third of the tails of normal young tadpoles, grows well and maintains its characteristic structure during early larval development, but regresses rapidly as the hosts approach metamorphosis. Carcinoma implants in the tails of nonmetamorphosing, thyroidectomized or hypophysectomized, tadpoles follow the same growth-regression sequence. The proportion of the effective total of implants that take and grow (53 to 60 per cent), the proportion that regress after growth (95 to 100 per cent), the rate of implant growth, the maximum size attained, and the rate of regression, are not significantly different in nonmetamorphosing tadpoles compared with normal control tadpoles.

The changes in the host tail that bring about tumor regression during later larval development are not known. Regression is associated with an accumulation of spindle-shaped mesenchyme cells, and occasionally of numerous small round cells, around the implant. This type of tissue response may be a causative factor. The present work indicates that this or other unknown factors are effective against cancerous as well as incompatible normal tissues, and are developed in the absence of thyroid or pituitary, and of the metamorphic alterations with which these glands are associated.

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Tissue Metabolism Studies on Bone Marrow

Consideration in Relation to Tumor Metabolism*

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Bone marrow cells, both myeloid and erythroid, are among the few that exhibit active multiplication in the adult. The metabolism of these cells is consequently of interest in connection with studies of normal and abnormal growth. It is the purpose of this paper to review certain pertinent data on bone marrow metabolism and to add new data permitting a consideration of bone marrow metabolism in relation to tumor metabolism.

Metabolism of Myeloid and Erythroid Cells

Normal rabbit bone marrow [1] consists, in addition to fat cells, of a mixture of myeloid and erythroid cells in approximately equal numbers. The former, however, average some 4 times the size of the latter, so that by far the larger part of the nonfatty tissue is myeloid. When slices of such normal marrow are suspended in serum average Q values, expressed in terms of fat-free dry weight calculated from nitrogen analyses, are $Q_{O_2} = -7$, $Q_G^{O_2} = 3$, $Q_G^{N_2} = 14$. It is possible, however, to distinguish between the metabolism of the myeloid and erythroid cells by comparing predominantly myeloid with predominantly erythroid marrows and making small extrapolations to 100 per cent myeloid and 100 per cent erythroid cells (22). The results are given in Table I, which also lists several of the derived metabolic quotients.

It is at once apparent that the myeloid cells are characterized by relatively active glycolytic mechanisms, both aerobic and anaerobic, whereas the erythroid cells exhibit a predominantly oxidative type of metabolism. It is also notable that the myeloid cells so closely meet the requirements of a tumor type of metabolism, as recently defined by Burk (2) and also listed in the table. Two additional criteria, however, the succinate and *p*-phenylenediamine tests of Craig, Bassett, and Salter (4) and the R. Q. are not shown in the table, but will be discussed in detail below.

Before passing on to these criteria, however, it appears desirable to comment briefly upon the aerobic glycolysis of marrow. Three points are worthy of note: In the first place, aerobic glycolysis is a relatively small but constant feature of the metabolism of normal marrow that appears to be due entirely to the metabolism of the myeloid cells (22). Secondly, it is not due to injury to the cells; see discussion in Fleischmann's paper (8). Lastly, it has about the same value in Ringer's solution as in serum, whereas respiration and anaerobic glycolysis are considerably higher in the latter medium (21). This makes aerobic glycolysis a disproportionately large feature of the metabolism in Ringer's solution and indicates the necessity of considering the suspension medium when attempting to draw a distinction between normal and tumor type metabolism.

Table I: Average Figures for Respiration and Glycolysis of Rabbit Bone Marrow Cells, with Derived Quotients

Cell type	Q_{O_2}	$Q_G^{O_2}$	$Q_G^{N_2}$	Meyerhof oxidation quotient	Absolute Pasteur effect	Fermentation excess (U)
Erythroid cells	−9	0	7	2.3	7	−11
Myeloid cells	−6	9	22	6.5	13	+10
Approximate limits (criteria) of a tumor type of metabolism (Burke, 2)	2–10±	0–15 ±	8–20 ±	3–6 ±	8–15 ±	−5 to +25 ±

Succinate and *p*-Phenylenediamine Tests

It is clear from the remarks above, that myeloid bone marrow cells exhibit metabolic characteristics that

* This investigation was aided by a grant from the John and Mary R. Markle Foundation.

[1] Most of the studies referred to in this paper were made on rabbit femoral bone marrow. The sole published paper on human marrow tissue metabolism (16) deals with respiration only. We are now accumulating respiration and glycolysis data on human marrow and the indications at present are that its metabolic characteristics closely resemble those of rabbit marrow.

closely resemble those of most malignant tumors. Craig, Bassett, and Salter (4) have put forward a criterion of malignancy based on the effect upon oxygen consumption of additions of succinate or *p*-phenylenediamine. These tests are interpreted as indicating "the gross effectiveness of the succinic dehydrase and cytochrome systems" in the cells. It had already been shown (6, 7, 17) that the activity of these enzyme systems is relatively low in certain tumors. The Salter group found that their normal tissues exhibited increases in Q_{O_2} of the order of 100 to 300 per cent upon addition of succinate and 200 to over 400 per cent upon addition of *p*-phenylenediamine, while most tumors studied, including the "artificially benign" tumors, exhibited poor responses. They noted also, however, that normal mammary tissue and both normal and leukemic leukocytes yielded poor responses to succinate while exhibiting good responses (though very variable in the case of mammary tissue) to *p*-phenylenediamine.

In the hope that these tests would enable us to make a clear differentiation between a normal and tumor type of metabolism we have applied them to various types of marrow, with the results shown in Table II.

The first part of the table shows the results obtained with the slices suspended in Ringer's solution, exactly after the technic described by Craig, Bassett, and Salter. Very poor increases in Q_{O_2} are noted upon addition of succinate, and even the responses to *p*-phenylenediamine are well below the normal criterion [2] of about 200 per cent. Lest these results be attributed to some error in technic we repeated the procedures with rat liver, and obtained responses in the same range as those reported by the Salter group. Finally, on the basis that the marrow might be damaged in Ringer's solution we repeated the tests in serum, with the even poorer responses noted in the table. We are forced to conclude that with normal bone marrow, as with normal leukocytes, the succinate and *p*-phenylenediamine tests are apparently of no value in aiding the distinction between a normal and tumor type of metabolism.

In further consideration of the general applicability of these tests it seemed desirable to study the responses of two other normal tissues, heart and kidney, in which particularly active cytochrome systems have been demonstrated (17). Two *p*-phenylenediamine tests with rabbit cardiac tissue yielded increases in oxygen consumption of 620 and 535 per cent, but the responses with kidney were definitely poor. In 8 experiments, 3 with rat and 5 with rabbit kidney slices, the average increase in oxygen consumption upon addition of succinate was 68 per cent (37 to 120 per cent) and with *p*-phenylenediamine 65 per cent (46 to 90 per cent). This result suggests an alternate interpretation of the tests; namely, that they measure the extent to which the enzyme systems concerned are saturated with substrate under the conditions of the experiment, rather than the "over-all activity" of these systems. One would then account for the results described above on the basis that whereas both tissues contain active cytochrome systems, in kidney but not cardiac tissue these are well supplied with substrate without addition of succinate or *p*-phenylenediamine. The implications of these findings will be considered in the discussion.

[2] Craig, Bassett, and Salter do not state precisely what is to be considered the normal range of response to the succinate and *p*-phenylenediamine tests. The criteria used in the present paper are those that appear to be warranted from their data.

TABLE II: SUCCINATE AND *p*-PHENYLENEDIAMINE TESTS ON MARROW

Experiment No.	Increase in oxygen consumption: With succinate, per cent	Increase in oxygen consumption: With *p*-phenylenediamine, per cent
IN RINGER-PHOSPHATE-GLUCOSE SOLUTION		
2	—	45
3	—	34
4	31	—
5	39	14
6	13	83
8	10	82
10 *	28	90
16 *	22	68
22 *	32	51
23 *	13	55
IN SERUM		
2	—	3
3	—	22
7	—	26
8	11	23

* Predominantly myeloid marrows; others normal.

THE RESPIRATORY QUOTIENT OF BONE MARROW CELLS

Included in Burk's list of criteria for a tumor type of metabolism is an R. Q. between 0.75 and 0.9±. The qualifications attending this inclusion will be discussed below; attention must first be given to the problems involved in measuring the R. Q. of marrow cells.

In a recent publication (24) the R. Q. of 5 normal marrows in serum, measured in Summerson differential manometers (18), was reported as varying between 0.91 and 1.13. Previously (21), with a less satisfactory apparatus, values from 0.88 to 0.94 were obtained in 5 experiments. Upon reinvestigation of this subject with Summerson manometers, for the present publication, values from 0.95 to as high as 1.26 were obtained, and we had also occasionally observed R. Q.'s as high as 1.2 in the past. While some of these figures

could be discounted on the basis of experimental error, the high trend was disturbing until the recent paper of Mirski (13) pointed out that certain adipose tissue in serum may have an R. Q. as high as 1.25 associated with incomplete breakdown of carbohydrate, although a synthesis of fat from carbohydrate should perhaps also be considered. This suggested that in normal marrow, with its high content of fat cells, similar processes might be occurring. Accordingly, the experiments now reported (Table III) [3] were made with suspensions of marrow cells prepared by teasing the marrow into small pieces in Ringer's solution, shaking vigorously in a test tube, centrifuging lightly, and removing the supernatant containing most of the fat cells before resuspending the marrow cells in serum. These procedures appear not to damage the cells appreciably (24), and with such material we have never obtained R. Q.'s above 1.03, as the table shows.

TABLE III: R. Q. OF RABBIT BONE MARROW SUSPENSIONS

Predominantly erythroid marrows					Predominantly myeloid marrows				
Experiment No.	Erythroid cells, per cent	R. Q. (1)	R. Q. (2)	R. Q. Av.	Experiment No.	Myeloid cells, per cent	R. Q. (1)	R. Q. (2)	R. Q. Av.
5	88	0.96	0.90	0.93	15	81	0.96	—	0.96
3	80	1.02	0.94	0.98	10	78	1.02	1.01	1.02
4	73	1.00	0.88	0.94	14	73	0.88	0.94	0.91
8	67	0.97	0.97	0.97	13	73	0.91	0.94	0.93
9	64	0.91	0.90	0.91	11	72	1.03	1.02	1.03
					12	67	1.03	0.92	0.98
					6	64	0.87	0.95	0.91
Average				0.95	Average				0.96

In order to determine whether the R. Q.'s of the myeloid and erythroid cells differ appreciably, the measurements were made mostly on marrows containing a preponderance of one cell type. Predominantly erythroid marrows were obtained by inducing a hemolytic anemia with phenylhydrazine (40 mgm. per kg. intraperitoneally). The animals were not sacrificed until 5 days after the drug had been injected. Under these conditions the marrow respiration and glycolysis are not affected except by virtue of the resulting erythroid hyperplasia (22). Predominantly myeloid marrows were obtained by producing intrapleural abscesses by the injection of 0.25 cc. of a 5 per cent solution of croton oil in olive oil 4 to 7 days before sacrifice of the animals.[4]

The R. Q. values listed in duplicate in Table III vary over the 0.9 to 1.03 range without significant relationship to the dominant cell type. One may conclude that the R. Q. of the myeloid cells is outside the 0.75 to 0.9± range included by Burk in his list of criteria for a tumor type of metabolism.

GLYCOLYSIS AND GROWTH

Metabolic studies on the erythroid (immature nucleated red) cells in bone marrow yield data pertinent to the frequently discussed relationship between glycolysis and growth. Whereas these cells under normal conditions are actively multiplying and maturing to supply the replacement demand for erythrocytes, under conditions of stress such as are occasioned by hemorrhage, hemolytic anemia, and low oxygen tension, the marrow becomes hyperplastic with erythroid cells that exhibit frequent mitotic figures and other evidences of multiplication and growth. Such tissue exhibits low rather than high glycolytic activity, and the small amount of aerobic glycolysis present may be attributed to the myeloid cells (22). Typical Q values for a marrow containing about 80 per cent erythroid cells are $Q_{O_2} = -8.0$, $Q_G^{O_2} = 1.5$, $Q_G^{N_2} = 11.0$. This is true whether the impetus to hematopoiesis is supplied by hemorrhage, hemolytic anemia, or low oxygen tension (23) and it is also notable that when such marrows are exposed *in vivo* to lowered oxygen tension there is no increased tendency to form lactic acid. Such marrows are, in fact, comparable to regenerating liver (14) since both exhibit active respiratory rather than glycolytic mechanisms. Erythroid marrow differs, however, in having an R. Q. of nearly unity, and is hence a good example of an actively growing tissue exhibiting low glycolysis and high R. Q. The data presented here provide further support for the view (1, 2, 14) that growth and glycolysis are not of necessity related.

DISCUSSION

The foregoing sections dealing with myeloid marrow have shown that this tissue has a respiratory and glycolytic metabolism remarkably similar to that of

[3] I am indebted to Dr. Margaret Austin for making many of the determinations reported in this table.

[4] I am indebted to Dr. Valy Menkin for suggesting this procedure, which he has frequently used (12) to produce sterile inflammatory reactions. The resulting myeloid marrow hyperplasia is much greater and more dependable than that obtained with other methods that have been used for the purpose (22).

most malignant tumors. This would make all the more difficult the effort to demonstrate metabolic differences between myeloid leukemic and comparable normal cells. Victor and Potter (20), Hall and Furth (9), and Burk and his collaborators (3) have shown that with spontaneous, but not methylcholanthrene-induced *lymphatic* leukemia, this demonstration is facilitated by the relatively low anaerobic glycolysis of normal lymphatic tissue. However, in view of the foregoing considerations, exception may be taken to the following statement of Kempner (10), "Whether leukemic cells are malignant or benign tumor cells, or normal young tissue cells, cannot be decided by morphological investigation. The question can be answered definitely by studies of the metabolic reactions of leukemic blood cells." The metabolic reactions referred to by Kempner are measurements of aerobic glycolysis, which he considers "may characterize either cancer metabolism or the dying off of any tissue within or without the body." I would add that it may also characterize various normal tissues, including myeloid cells. On the other hand, I agree that metabolic studies are of the utmost importance in attempting to gain an understanding of the fundamental abnormal processes in cancer, but it would appear desirable, particularly in the cases of myeloid leukemia, to direct attention to specific metabolic processes rather than to over-all respiratory measurements. The recent important paper of Dickens and Weil-Malherbe (5) is an example of this type of approach. These authors show that certain malignant liver tumors, in which respiration is not impaired (although aerobic and anaerobic glycolysis is elevated), nevertheless exhibit greatly impaired ability to carry out specific chemical processes, including urea formation and oxidation of uric acid.

Concerning the results with the succinate and *p*-phenylenediamine tests, we find that normal rabbit bone marrow and kidney give poor responses (malignant type metabolism) while Craig, Bassett, and Salter (4) report that both normal and leukemic leukocytes give good responses to *p*-phenylenediamine, though poor responses to succinate. Nevertheless, Roskelley, Horwitt, and Salter (15) find the tests useful in distinguishing normal from malignant human kidney tissue. This confusing state of affairs, in addition to the questionable theoretical basis of the tests, raises some doubt respecting their general applicability as useful supplements of the customary morphologic and metabolic criteria for distinguishing between normal and malignant tissues.

The relatively high R. Q. of myeloid marrow found in this paper is the only metabolic criterion so far studied that places this tissue outside the malignant class. This result should not be interpreted as implying that the R. Q. is generally of greater value than the other metabolic criteria, for the reverse is more nearly true (2). There is, in fact, considerable doubt whether the R. Q. of malignant tissues is usually lower than that of their normal homologues. In the case of hematopoietic tissue this question has been studied principally with reference to leukemia in mice, a subject that has recently been exhaustively reviewed by Burk and his collaborators (3). It seems clear that in some, but not all, spontaneous *lymphatic* leukemias the R. Q. of the malignant lymphatic tissue is lower than that of the normal. This difference is not found in the induced leukemias so far investigated.

There is a paucity of data on the R. Q. of myeloid leukemic cells. A few high, intermediate, and low values are listed in the review cited above. Kempner and Gaffron (11) report an R. Q. of 0.75 in a single case of myeloblastic leukemia in man. The R. Q. of rabbit exudate leukocytes is about 0.85 (19). It is clear that the available data are both insufficient and too questionable in accuracy to permit a generalization as to the value of the R. Q. in distinguishing normal from leukemic tissue.

SUMMARY AND CONCLUSIONS

Bone marrow respiration and glycolysis have been reviewed with particular reference to the eight criteria of a tumor type of metabolism listed by Burk (2). Myeloid, but not erythroid cells, fulfill seven of the eight criteria—only the relatively high R. Q. (about 0.96) serves to distinguish these cells metabolically from malignant cells. The succinate and *p*-phenylenediamine tests of Craig, Bassett, and Salter (4) appear not to be of value in this connection and their general applicability is questioned. Also, more evidence is presented to support the view that growth and glycolysis are not necessarily related. The implications of these studies with reference to the metabolism of leukemic cells is discussed.

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Abstracts

Experimental Research, Animal Tumors

Carcinogenic Action of Two Azo Compounds in Mice. Andervont, H. B., and Edwards, J. E. [*Nat. Cancer Inst., Bethesda, Md.*] J. Nat. Cancer Inst., **3**:349-354. 1943.

Olive oil solutions of *o*-aminoazotoluene or *p*-dimethylaminoazobenzene were administered subcutaneously to mice of strains C, C57 black, C3H, and A. Hepatic changes, hepatomas, pulmonary tumors, hemangioendotheliomas, and fibrosarcomas at the site of injection were induced by *o*-aminoazotoluene. The strains differed somewhat in the type of tumors developed, and females appeared more susceptible to liver damage than males of the same strain. Olive oil solutions or glycerol suspensions of *p*-dimethylaminoazobenzene were much less carcinogenic than similar preparations of *o*-aminoazotoluene under the same conditions of administration.—H. Q. W.

Response of Strain A Female Mice to Small Amounts of *o*-Aminoazotoluene. Andervont, H. B., and Edwards, J. E. [*Nat. Cancer Inst., Bethesda, Md.*] J. Nat. Cancer Inst., **3**:355-358. 1943.

An experiment was planned to determine the minimum amount of *o*-aminoazotoluene that, when administered by subcutaneous injection to female strain A mice, would produce liver or other tumors. It was found that a single dose of 10 mgm. would induce cirrhosis within 27 weeks, and hepatomas and pulmonary tumors within 35 weeks. Doses of 20, 30, 40, 50, or 60 mgm. induced the same changes more promptly, and, in addition, caused hemangioendotheliomas.—H. Q. W.

The Fluorescence of 3:4-Benzpyrene in Vivo. Part I. The Distribution of Fluorescence at Various Sites, Especially the Skin of Mice. Doniach, I., Mottram, J. C., and Weigert, F. [*Mt. Vernon Hosp., Northwood, Middlesex, England*] Brit. J. Exper. Path., **24**:1-9. 1943.

A technic is described for producing fluorescence spectrograms of biological specimens. Benzpyrene (BP) painted on the skin of mice is transformed within 1 or 2 days into a derivative with blue fluorescence (spectrum maxima at 450 and 425 mμ.). This spectrum resembles that of the orthorhombic metastable crystals of BP, but other evidence indicates that the two substances are not identical. The derivative is soluble in alkali (blue fluorescence) and becomes ether-soluble from an acid watery medium. It is precipitated by half-saturation ammonium sulfate from an alkaline extract of BP-painted skin, is probably phenolic, but is not identical with 6- or 4-hydroxybenzpyrene. The fluorescence spectrum is not identical with that of the hydroxybenzpyrene (green fluorescence in alkaline solution) that Chalmers and Crowfoot isolated from the feces of BP-treated animals and that they assumed to be identical with the derivative called "BPX" by Peacock.

After intravenous injection of colloidal BP into mice and rabbits, the derivative can be detected in the cortex of the kidney, in the lungs, liver, intestine, and mammary gland. The evidence concerning the latter organ is provided by the spectrum of extracts of milk taken from the stomachs of sucklings of mothers injected with BP.

Observations by microscopy in ultraviolet light are recorded of the behavior of ciliates such as *Paramecium*, etc., towards colloidal suspensions of BP.

If mouse skin is painted with BP the hydrocarbon is no longer extractable after 48 hours, but the blue fluorescing derivative appears in a few hours, increases to a maximum at the 4th to 6th day, and persists for 2 to 3 weeks. It appears at the site of painting with BP and not elsewhere on the skin, thus indicating that the transformation occurs locally. It is concentrated in the epithelial cells of the hair bulbs, which form a continuous layer with the Malpighian layer from which tumors arise.

The persistence and distribution of the derivative in the skin, and its appearance in those organs (kidney excepted) liable to the induction of cancer by BP, suggest that this derivative represents an intermediate stage in the production of tumors by BP.—I. H.

The Fluorescence of 3:4-Benzpyrene in Vivo. Part II: The Inter-Relationship of the Derivatives Formed in Various Sites. Doniach, I., Mottram, J. C., and Weigert, F. [*Mt. Vernon Hosp., Northwood, Middlesex, England*] Brit. J. Exper. Path., **24**:9-14. 1943.

Five series of mice were treated by: (1) feeding with benzpyrene (BP); (2) intravenous injection with BP; (3) feeding with "BPX" (see abstract immediately preceding this); (4) feeding with BP after the common bile duct had been ligated and cut; (5) intravenous injection with BP after this operation. Examination of the tissues in ultraviolet light showed that BPX is not absorbed from the intestine and that substances with much the same blue fluorescence (spectrum maxima near 450 and 425 mμ.) are present in (a) tissues: kidney cortex, liver, lung, skin (after painting only), walls of stomach and intestine; and milk, (b) bile, and (c) plasma. The authors suggest that the relation between "tissue-BP-blue," "bile BPX," and "plasma BPX," "is possibly due to the linking of the same blue fluorescent benzpyrene derivative as a prosthetic group to various cell constituents."—I. H.

Sebaceous Glands and Experimental Skin Carcinogenesis in Mice. Simpson, W. L., and Cramer, W. [*Barnard*

Free Skin and Cancer Hosp., St. Louis, Mo.] CANCER RESEARCH, **3**:515-518. 1943.

Fluorescence microscopic studies of mouse skin have shown that the sebaceous glands absorb much of a benzene solution of methylcholanthrene and subsequently pour out sebum containing the carcinogen onto the surface of the skin. The authors have now studied the effects of single and multiple applications to mouse skin of 20-methylcholanthrene dissolved in wool fat (anhydrous lanolin), a vehicle chosen as most likely to resemble mouse sebum.

Two experiments, comprising a total of 110 Swiss mice, were carried out by applying a 0.3% solution of the carcinogen 3 times weekly for 14 weeks. In these experiments the lanolin almost completely prevented the carcinogenic activity of methylcholanthrene. The mice did not become epilated; there was no hyperplasia of the epidermis or hair follicles; the sebaceous glands, which are usually destroyed rapidly by benzene solutions of the carcinogen, were still present after 42 applications, though small and less numerous. Six months after the first painting, no neoplasms had appeared except for one precancerous papilloma in a mouse that died and 2 small papillomas in surviving animals. In this same strain similar treatment with the carcinogen in benzene leads to the development of malignant tumors in all survivors at 6 months. If a similarity of mouse sebum and sebum from sheep (anhydrous lanolin) may be assumed, these results suggest the provisional conclusion that the sebaceous glands are a protective mechanism against the carcinogenic action of methylcholanthrene.—Authors' abstract.

Quenching of Fluorescence by Nitric Oxide. Weil-Malherbe, H., and Weiss, J. [*Royal Victoria Infirmary and Univ. of Durham, Newcastle-on-Tyne, England*] NATURE, **151**:449. 1943.

The quenching of the fluorescence of anthracene, benzpyrene, and methylcholanthrene can be carried out by nitric oxide as well as by oxygen. The nitric oxide effect is reversed by replacing the gas with N_2. Irradiation of the NO–hydrocarbon complex with ultraviolet light leads to the formation of irreversible nitrogen-containing compounds. (See abstract of previous paper by the same authors, CANCER RESEARCH, **2**:734. 1942).—I. H.

Effect of Certain Split Products of Carcinogenic Azo Dyes on Melanin Formation. Baker, A. K., Kline, B. E., and Rusch, H. P. [*Univ. of Wisconsin Med. Sch., Madison, Wis.*] PROC. SOC. EXPER. BIOL. & MED., **50**:361-363. 1942.

This is a preliminary report of a study of the effect of certain split products of some carcinogenic azo dyes and related compounds on melanin formation.

Melanin formation was not obtained with the following non-autoxidizable compounds: *p*-aminoacetanilide, β-naphthylamine, *p*-aminobenzoic acid, and sulfanilamide. Yet when the chemically related autoxidizable compounds, *p*-aminodimethylaniline, *p*-phenylenediamine, methyl-*p*-phenylenediamine, and *p*-aminophenol, were used, the color changes in both tyrosine-tyrosinase and control solutions were similar. It is, therefore, difficult to interpret the action of these latter chemicals on melanin formation.—M. B.

Incubation of Citrulline and Ammonia with Normal and Neoplastic Hepatic Tissues. Greenstein, J. P. [*Nat. Cancer Inst., Bethesda, Md.*] J. NAT. CANCER INST., **3**:293-296. 1942.

Since many of the specific functions of tissues are diminished when they become neoplastic, and since one important function of the liver is the synthesis of urea, the author compared the synthesis of urea from citrulline and ammonia by normal rat liver and by transplanted rat hepatoma 31. He found that the hepatoma failed to synthesize any urea under conditions whereby slices of normal liver synthesized urea rapidly. Slices, but not extracts, of both normal liver and hepatoma took up ammonia in the absence of citrulline, the normal liver being more active than the tumor.—H. Q. W.

Attempts to Induce Stomach Tumors. I. The Effect of Cholesterol Heated to 300° C. Kirby, A. H. M. [*Glasgow Royal Cancer Hosp., Glasgow, Scotland*] CANCER RESEARCH, **3**:519-525. 1943.

Cholesterol heated to 270–300° C. for half an hour in air was fed at a level of 20 mgm. daily to albino rats up to 2 years. No significant lesion, from the point of view of carcinogenesis, was observed in either part of the stomach. The role of diet in the production of stomach lesions is discussed. Preliminary observations regarding pyrolytic decomposition of cholesterol are recorded, including the formation of a substance having a blue fluorescence in the ultraviolet beam.—Author's summary.

The Influence of Caloric Restriction upon the Incidence of Spontaneous Mammary Carcinoma in Mice. Visscher, M. B., Ball, Z. B., Barnes, R. H., and Sivertsen, I. [*Univ. of Minnesota, Minneapolis, Minn.*] SURGERY, **11**: 48-55. 1942.

Fifty-one C3H mice were fed in unrestricted amount a diet of glucose, lard, casein, dry yeast, dry alfalfa leaf, and salt mixture. Forty-four animals received a similar diet but with restriction of carbohydrates and fat so that the total caloric intake was decreased by about one-third. After 16 months 32 mice on the unrestricted diet had developed mammary carcinoma and 15 were tumor-free. Of the mice on the restricted diet 25 survived 16 months and none had mammary tumor.—W. A. B.

Vitamin C and Tumor Growth. Brunschwig, A. [*Univ. of Chicago, Chicago, Ill.*] CANCER RESEARCH, **3**:550-553. 1943.

Vitamin C was injected into mice and rats bearing transplantable tumors (melanosarcoma S39, Crocker sarcoma 180) and was observed to stimulate tumor growth mildly in some instances. In some groups of animals this stimulatory effect on the tumors was not demonstrable.—Author's abstract.

Inositol a Tumor Growth Inhibitor. Laszlo, D., and Leuchtenberger, C. [*Mt. Sinai Hosp., New York, N. Y.*] SCIENCE, **97**:515. 1943.

Inositol was given intravenously in doses from 38 to 1,000 γ to female Rockland mice carrying sarcoma 180. The degree of inhibition depended on the dose. The mean terminal tumor weight of the mice receiving the highest dose was about one-third that of the mice with the lowest dose, or of the controls (saline). Sodium phytate

and lipositol showed an inhibition similar to that of inositol.

Subcutaneous or oral administration of inositol was without effect. Also ineffective were intravenous injections of *l*-inositol, inosose, and crystalline factors of the vitamin B complex.—M. B.

Influence of Vitamin B_6 and Pantothenic Acid on Growth of Sarcoma 180. Bischoff, F., Ingraham, L. P., and Rupp, J. J. [*Santa Barbara Cottage Hosp. Research Inst., Santa Barbara, Calif.*] Arch. Path., **35**:713-716. 1943.

In 3 experiments (122 Marsh-Buffalo mice), a synthetic diet containing vitamins of the B group other than B_6 produced a significant decrease in the rate of tumor growth, which was corrected by the addition of vitamin B_6 to the diet; and in a single experiment (30 mice) the addition of vitamin B_6 to a diet otherwise completely deficient in the B complex produced a significant increase in tumor growth. The findings are considered to establish the essentiality of vitamin B_6 for the maximum growth of sarcoma 180.

Pantothenic acid deficiency was without influence on the tumor in 31 mice.—J. G. K.

Further Studies of the Liver Catalase Activity of Tumor-Bearing Animals. Greenstein, J. P. [*Nat. Cancer Inst., Bethesda, Md.*] J. Nat. Cancer Inst., **3**:397-404. 1943.

Extracts of normal rat liver were incubated at different temperatures with extracts of transplanted Jensen sarcoma, and with serum and extracts of other tissues of tumor-bearing rats. Similarly, rat liver slices were incubated with tumor slices, and extracts of normal mouse liver with extracts of sarcoma 37. None of these mixtures affected the catalase activity of the livers. Thus tumor tissue apparently has no direct action *in vitro* on liver catalase.

Dialysis at low temperatures of extracts of normal rat liver and of the livers of tumor-bearing rats caused the same proportionate drop in the catalase activity of both extracts. This fact indicates the absence of readily dissociable inhibitor from the liver catalase of the tumor-bearing animals.

Aqueous extracts were prepared at the same concentrations from livers of normal and of tumor-bearing rats. On dilution of the extracts from the livers of normal animals with boiled normal liver extract in the ratio of 1:2.2, values for catalase activity were obtained similar to those of the undiluted extracts of the tumor-bearing animals. The rates of reaction of such extracts with hydrogen peroxide were practically identical, and the drop in activity in each on dialysis was the same.

Extracts of a transplanted hepatoma injected intraperitoneally into normal rats produced no change in the liver catalase activity of these animals.

The view is advanced that the low liver catalase activity of tumor-bearing animals is ascribable to the presence of only about half the normal amount of total catalase in this organ.—F. L. H.

Tumor Enzymology. Greenstein, J. P. [*Nat. Cancer Inst., Bethesda, Md.*] J. Nat. Cancer Inst., **3**:419-447. 1943.

The paper presents a comprehensive summary of enzyme data relevant to the cancer problem. The enzymatic activity of tumors is compared with that of the normal tissues of origin. The tumors studied in this manner include hepatomas, lymphomas, mammary tumors, rhabdomyosarcomas, adenocarcinomas of the stomach and intestines, carcinomas of the prostate, and osteogenic sarcomas.

The enzymatic activity and the concentrations of certain components of the tissues of normal animals are compared with those of tumor-bearing animals. The study includes liver, kidney, spleen, adrenals, and muscle, as well as blood and serum. The observations indicate that the systemic effects elicited by the tumor generally parallel in degree the growth of the tumor and are reversible with removal of the tumor.—F. L. H.

Note on the Copper Content of the Tissues of Tumor-Bearing Animals. Greenstein, J. P., and Thompson, J. W. [*Nat. Cancer Inst., Bethesda, Md.*] J. Nat. Cancer Inst., **3**:405-408. 1943.

Values for the copper content of tissues of tumor-bearing and normal animals are compared. The copper content of the whole blood of tumor-bearing rats was lower than that of normal rats and unequally distributed between cells and serum. The copper content of normal and regenerating rat livers was the same, but that of the livers of tumor-bearing rats was distinctly higher than normal. Normal mouse livers were considerably higher in copper content than normal rat livers, but the increase in copper in the livers of tumor-bearing mice over that of the normal was less than in rats. The kidneys of normal rats and mice had a higher copper content than the livers of these species. In tumor-bearing animals, however, the copper content of the kidneys decreased as compared with values in normal animals.—F. L. H.

Hydrolysis of Glutathione by the Cathepsins of Normal Rat Tissues and Rat Hepatoma 31. Mayer, M. E., and Thompson, J. W. [*Nat. Cancer Inst., Bethesda, Md.*] J. Nat. Cancer Inst., **3**:383-387. 1943.

Cathepsins prepared from normal rat livers, livers of rats resistant to hepatoma 31, normal spleen and kidney, and hepatoma 31 hydrolyzed the glycine bond of glutathione at an optimum pH of 4.5.

The order in which the peptide bonds of glutathione were attacked was proved by the absence of free cysteine and the separation of γ-glutamylcysteine and glycine from the digests when the alkalimetric titration indicated that the equivalent of one peptide bond had been hydrolyzed.

The cathepsin from normal rat livers hydrolyzed the glycine peptide bond of glutathione at a rate twice that of the hepatoma cathepsin. But the hepatoma cathepsin was able to hydrolyze slowly the remaining γ-glutamylcysteine while the normal liver cathepsin did not attack this dipeptide. The normal spleen cathepsin also hydrolyzed both bonds of glutathione and at a much more rapid rate than did the hepatoma cathepsin. The rate of hydrolysis of glutathione by the cathepsin from livers of resistant rats was very slightly higher than by the cathepsin from normal rat livers. The rate of the kidney cathepsin was about one-half that of the normal liver cathepsin.—F. L. H.

Cytochrome Oxidase and *d*-Amino Acid Oxidase in Tumor Tissue. Shack, J. [*Nat. Cancer Inst., Bethesda, Md.*] J. Nat. Cancer Inst., **3**:389-396. 1943.

The activity of cytochrome oxidase and *d*-amino acid oxidase in a number of tumor and normal tissues was

measured. Particular attention was given to tissues of hepatic origin.

The ratio of cytochrome oxidase activity of normal liver to hepatoma was about 4 or 5, to regenerating liver 1, to fetal liver 2.5, and to liver of tumor-bearing animals about 1.1. A variety of other tumors possessed low cytochrome oxidase activities of the same order of magnitude as hepatoma.

The ratio of *d*-amino acid oxidase activity of rat liver to hepatoma 31 was about 10, to regenerating liver 1.2, to fetal liver 7, and to liver of rats bearing hepatoma 31 about 1.5. Neither mouse liver nor mouse hepatomas exhibited measurable *d*-amino acid oxidase activity.

The significance of these results to oxygen utilization by tumor tissue is discussed.—F. L. H.

The Action of Bacterial Toxins on Tumors. I. Relationship of the Tumor-Hemorrhagic Agent to the Endotoxin Antigens of Gram-Negative Bacteria. Zahl, P. A., Hutner, S. H., Spitz, S., Sugiura, K., and Cooper, F. S. [*Memorial Hosp., and Haskins Labs., New York, N. Y.*] Am. J. Hyg., **36**:224-242. 1942.

Injection of culture filtrates, or suspensions, of certain bacteria into tumor-bearing animals may induce severe hemorrhage in the tumor, frequently followed by complete regression of the neoplasm. The effect is especially pronounced with transplanted tumors but has been observed also with tar-induced and certain spontaneous tumors.

In the present work about 100 strains of bacteria, representing a number of principal genera, were examined in respect to their ability to elaborate tumor hemorrhage-producing materials. Both bacterial filtrates and suspensions were tested in mice bearing the transplantable sarcoma 180. Organisms producing tumor hemorrhagic materials were found to be characterized by the following common features: (1) They are gram-negative; (2) they contain complex endotoxin antigens; and (3), their pathogenesis is marked by vascular damage, disturbances in carbohydrate metabolism, and enteric irritation. Recent studies of certain endotoxin nonprotein O antigens leads to the conclusion that tumor-hemorrhagic agents produced by many gram-negative bacteria are probably identical with a polypeptide compound of the complex endotoxin antigens.—A. C.

Role of Thrombocytopenia in Hemorrhage Produced in Sarcoma 37. Shimkin, M. B., and Zon, L. [*Marine Hosp., Baltimore, Md.*] J. Nat. Cancer Inst., **3**:379-382. 1943.

Thrombocytopenia produced by anti-mouse-platelet serum, of the same level as that produced by a concentrate of *Bacillus prodigiosus* filtrate and by moccasin venom, did not produce hemorrhage in transplanted sarcoma 37 in strain A backcross mice. The action of the bacterial filtrate and of the snake venom on the transplanted sarcoma 37 is primarily that of an endothelial toxin.—F. L. H.

The Growth of Alien Strain Tumors in Parabiotic Mice. Harris, M. [*Wistar Inst., Philadelphia, Pa.*] Cancer Research, **3**:546-549. 1943.

Mice of similar strains were united by means of parabiosis, and inoculated with alien mouse tumors known to induce an immunity in the hosts. Primary injection of tumor into the left parabionts, 25 days after operation, resulted in rapid proliferation and growth of the implanted fragments. Inoculation of the same tumor 10 days later into the opposite parabionts was not followed by any perceptible growth of the implanted cells. It is suggested that inoculation of an immunizing tumor into one parabiont leads to simultaneous development of resistance in both animals.—Author's abstract.

Yolk Sac Cultivation of Tumors. Taylor, A., Hungate, R. E., and Taylor, D. R. [*Univ. of Texas, Austin, Tex.*] Cancer Research, **3**:537-541. 1943.

A method is described whereby tumors from the mouse and rat can be cultivated in the yolk sac of the developing chick embryo. Rapidly growing neoplastic tissue is dispersed and suspended in 0.85% saline solution and then injected by means of a hypodermic syringe into the yolk sac of an embryo at the fifth day of development. The inoculated egg is incubated for another 12 to 13 days, for a total of 17 to 18 days. The yolk sac tumor, which may attain a weight of several grams, resembles the donor material both in the gross and microscopically, and is generally located just beneath the area known as the umbilicus. Dba mouse mammary carcinomas, both spontaneous and transplanted, and the Walker rat carcinosarcoma 256 have been grown successfully in this manner.—Authors' abstract.

The Effect of Yolk Sac-Cultivated Tumors on the Hemoglobin Level in the Embryonic Chick. Taylor, D. R., McAfee, M., and Taylor, A. [*Univ. of Texas, Austin, Tex.*] Cancer Research, **3**:542-545. 1943.

A study was made of the effect of yolk sac-grown mammary carcinomas of dba mice on the hemoglobin level of 51 white Leghorn embryos that served as hosts for the tumors. The results obtained demonstrated a notable decline in the hemoglobin level of the experimental embryos. The severity of the effect tended to be in direct relation to tumor size, although a completely consistent, straight line relationship was not observed. Any growth of carcinomatous tissue (even as little as 0.03 gm.) in the yolk sac effected a measurable decrease in blood hemoglobin concentration. Individual tumors induced depression of hemoglobin level by as much as 70%. These results strengthen the conclusion reached previously in a similar investigation reported from this laboratory, in which mice and rats were used as the experimental animals; *i. e.*, tumors exert a direct inhibitory action upon the blood hemoglobin of the host.—Authors' abstract.

Specific Substances in the Urine of Leucemia Patients. Miller, F. R., Hause, W. A., and Jones, H. W. [*Jefferson Med. Coll., Philadelphia, Pa.*] Proc. Soc. Exper. Biol. & Med., **50**:115-116. 1942.

Urine from patients with chronic myeloid leukemia was extracted with chloroform, the latter removed by distillation, and the residue suspended in 200 to 300 cc. of 10% NaOH. This suspension was extracted 8 to 10 times with 100 cc. portions of ethyl ether. The ethyl ether-soluble fraction (A) was recovered by removal of the solvent. The residual alkaline solution (B) was reacidified with 30 to 50 cc. of concentrated HCl, extracted with chloroform, and after the removal of the chloroform, extracted with successive portions of petroleum ether (C); these extracts were then combined and distilled *in vacuo*.

Four guinea pigs receiving fraction B showed proliferation of myeloid cells. Three animals receiving fraction A showed no such proliferation. Five guinea pigs given fraction C showed, on autopsy, proliferation of myeloid cells in the liver, lungs, spleen, and adrenals. Blood smears showed 10 to 20% myelocytes.

Three similar fractions from urine of patients with chronic lymphoid leukemia showed proliferation of lymphoid cells with no apparent variation.

Urine of normal animals yielded fractions which gave no specific cellular response.—M. B.

Distribution of Alkaline Phosphatase in Normal and in Neoplastic Tissues of the Nervous System. A Histochemical Study. Landow, H., Kabat, E. A., and Newman, W. [*Coll. of Physicians and Surgeons, and Neurological Inst., New York, N. Y.*] Arch. Neurol. & Psychiat., **48**:518-530. 1942.

The method of Gomori and of Takamatsu was used for the demonstration of alkaline phosphatase in histological preparations. Tissues from mouse, cat, chicken, and man were studied. In normal tissues, alkaline phosphatase was found to be present in the endothelium of the blood vessels of the central nervous system and in the arachnoid. In the parenchyma of the nervous system, the amount of phosphatase activity was found to vary in different localities and in the same locality in different species, but, except in the chicken, the parenchymal reaction was much less striking than that of the vascular endothelium and the arachnoid. The suggestion is made that the phosphatase in the vascular endothelium may play a role in the passage of dextrose through the capillary wall, a view similar to that advanced by Lundsgaard to explain the transfer of dextrose through the intestinal wall and the convoluted tubules of the kidney.

Phosphatase activity was demonstrated in a number of common tumors of the nervous system, more frequently in meningiomas and in astrocytomas. Apparently the phosphatase content of tumors of the nervous system can be correlated roughly with that of the homologous normal tissue and with the tendency of the tumor to become calcified. The method has a limited usefulness in diagnosis of tumors when employed in conjunction with other technics.—A. C.

Studies of Normal and of Abnormal Mitotic Activity. II. The Rate and the Periodicity of the Mitotic Activity of Experimental Epidermoid Carcinoma in Mice. Blumenfeld, C. M. [*Cleveland City Hosp. and Western Reserve Univ., Cleveland, Ohio*] Arch. Path., **35**:667-673. 1943.

Squamous cell carcinomas produced experimentally with methylcholanthrene in 60 male CBA mice were procured at stated times during the day and night and fixed immediately in Bouin's fluid, together with normal epidermis from the same animals. Detailed histological studies showed that mitotic activity in the cancer cells remained at a practically constant level throughout the day and night, whereas the normal epidermal cells manifested the characteristic diurnal rhythm. The rate of mitotic activity in the carcinomas proved no greater than the maximum rate in an equal volume of normal epidermis. Certain implications of the findings are discussed. —J. G. K.

Cytology of Hepatic Tumors and Proliferating Bile Duct Epithelium in the Rat Induced with *p*-Dimethylaminoazobenzene. Dalton, A. J., and Edwards, J. E. [*Nat. Cancer Inst., Bethesda, Md.*] J. Nat. Cancer Inst., **3**:319-329. 1942.

A cytologic study of various lesions of the livers of Buffalo rats fed *p*-dimethylaminoazobenzene was made. In all neoplasms derived from the hepatic parenchymal cell, the Golgi apparatus had shifted to a completely juxtanuclear position. The type of mitochondria was found to vary from lesion to lesion, one mitochondrial form predominating in any one neoplasm. With some exceptions spherical mitochondria were characteristic of hepatoma type I. Tenuous, fine, filamentous mitochondria were characteristic of hepatoma type II.

Cytologic evidence indicates that the transplantable hepatoma 31 originated as a primary hepatoma of type II, and that the hepatic adenocarcinoma of the rat is derived from hepatic parenchymal cells rather than from cells of proliferating bile duct epithelium.—F. L. H.

Human Neoplasms in Tissue Culture. II. Observations upon Cells Derived from Peritoneal and Pleural Effusions. Coman, D. R. [*Univ. of Pennsylvania Med. Sch., Philadelphia, Pa.*] Cancer Research, **3**:526-530. 1943.

Cells derived from pleural and peritoneal effusions were grown in tissue culture by the roller tube method. Macrophages, polymorphonuclear leukocytes, lymphocytes, mesothelial cells, and fibroblasts were cultured from all fluids. In one instance endothelial cells were found, and these produced structures resembling capillaries. Cells from carcinomas and sarcomas were cultured and grew vigorously, thereby indicating that such cells remain viable and capable of proliferation after floating in pleural or peritoneal fluids if given a satisfactory surface to which they may become attached. Thus support is given to the view that carcinomatosis of serous membranes can occur by implantation. Small colonies were observed to develop from single neoplastic cells that had become isolated in the supporting plasma of the tissue culture. The significance of this observation is discussed as opening a field for further exploration. It is suggested that the culture of cells from pleural and ascitic fluids can be of aid in diagnosis under favorable circumstances.—Author's abstract.

Nucleolar Vacuoles in Living Normal and Malignant Fibroblasts. Lewis, W. H. [*Wistar Inst., Philadelphia, Pa.*] Cancer Research, **3**:531-536. 1943.

Many hundred cultures of normal and malignant fibroblasts from rat and mouse tissues were made in various media and examined for nucleolar vacuoles. Some cultures of normal fibroblasts had no nucleolar vacuoles, some had a few or a moderate number, and some had many cells containing them. Malignant fibroblasts from some tumors had no nucleolar vacuoles, those from other tumors had a few or a moderate number, and those from a few had many cells with them. No consistent correlations were found in either normal or malignant cells between the number of cells with nucleolar vacuoles and the culture medium, the extent of migration, the life of the culture, the number of mitoses, the amount of pinocytosis, or any cytological feature—such as the number and size of the nucleoli, the condition of the nucleo-

plasm, the number of nuclei, the number of fat globules, the mitochondria, the neutral red-staining vacuoles and granules, and the size of the central area. Normal fibroblasts had 1 to 30 and malignant ones 1 to 60 vacuoles per nucleolus. The number of vacuoles per nucleolus usually varied directly with the number of cells containing them and with the size of the nucleolus. The relative number of cells with nucleolar vacuoles may increase or decrease during the life of a culture. Malignant fibroblasts cannot as a rule be distinguished from normal ones by the relative number of cells with nucleolar vacuoles, by the number of vacuoles per nucleolus, or by the size of the vacuoles.—Author's abstract.

Origin of Malignant Tumour Cells. Koller, P. C. [*Univ. of Edinburgh, Edinburgh, Scotland*] NATURE, **151**: 244-246. 1943.

A cytological investigation of the nucleus and chromosomes was carried out on 565 human tumors (carcinoma of the skin, esophagus, colon, rectum, larynx, lung, cervix, uterus, and breast). The characteristic abnormalities exhibited by malignant cells such as polyploid, multinucleate, and giant cells, multipolar spindles, stickiness, and displacement of chromosomes at metaphase, as well as increased rate of division, are attributed to a quantitative change in nucleic acid synthesis. Since "it is known that the heterochromatic regions of chromosomes primarily concerned with nucleic acid synthesis can undergo spontaneous mutation and structural change more easily than other parts" it is suggested that a gene mutation in such a chromosomal region may initiate the alteration in nucleic acid metabolism. The ultimate cause of the somatic mutation is unknown. "The cytological analysis reveals only the fact that in the tumour cell there is a disturbed nucleic acid metabolism."—R. J. L.

Effects of X-Rays and Neutrons on Mouse Lymphoma Chromosomes in Different Stages of the Nuclear Cycle. Marshak, A. [*Univ. of California, Berkeley, Calif.*] RADIOLOGY, **39**:621-626. 1942.

Marshak counted the relative numbers of normal and abnormal mitotic figures present in transplantable mouse lymphoma at various time intervals after exposure to x-rays and to neutrons. There was a sharp increase in the percentage of abnormal mitoses 3 hours after exposure to x-rays and to neutrons and a greater increase at 12 hours. Cells observed in mitoses at 12 hours must have been in the resting stage at the time of exposure, and hence the cells of this lymphoma differ from those of tumors previously investigated in that their radiosensitivity is maximal during the resting phase of the nuclear cycle and not in early prophase. As the dose of x-rays or neutrons was increased, it was found that the percentage of normal mitoses decreased as a negative exponential function of the dose, indicating that the damage resulted from a single encounter of the effective agent with a sensitive portion of the chromosome and not from the gradual accumulation of diffusible toxic substances.

The relative efficiency of neutrons as compared to x-rays in producing nuclear damage was not constant when calculated at different time intervals but was maximal at 12 hours after exposure, indicating that nuclei irradiated at one stage during the resting phase were relatively more vulnerable to neutrons than to x-rays.

It is suggested on the basis of these findings that neutron radiation may prove effective in treating some tumors that are resistant to x-ray therapy.—C. E. D.

The Concentration of P^{32} in Some Superficial Tissues of Living Patients. Marinelli, L. D., and Goldschmidt, B. [*Memorial Hosp., New York, N. Y.*] RADIOLOGY, **39**:454-463. 1942.

A patient with cutaneous melanoma and 2 patients with mycosis fungoides were given radioactive phosphorus by mouth. Determinations of the radioactivity of the superficial tissues were made with a special Geiger-Müller counter. In all 3 patients the radioactivity was greater in the region of the skin lesions than in other parts of the body surface. The variations of radioactivity in various parts of the body, as a function of time, are shown in 4 charts.—C. E. D.

A Comparative Histological Study of the Anterior Hypophyses and the Ovaries of Two Strains of Rats, One of Which Is Characterized by a High Incidence of Mammary Fibroadenoma. Wolfe, J. M., and Wright, A. W. [*Albany Med. Coll., Union Univ., Albany, N. Y.*] CANCER RESEARCH, **3**:497-508. 1943.

Anterior hypophyses and ovaries from rats of the Albany strain, in which the incidence of spontaneous mammary fibroadenomas is high, were compared histologically with those of the Vanderbilt strain, in which such tumors rarely occur. Rats ranging in age from 1 to 28 months were used. In all age groups the anterior hypophyses of the Albany rats were characterized by significantly lower percentages of eosinophils and higher percentages of chromophobes than were found in the Vanderbilt rats. The relative numbers of basophils were practically the same in the two strains. In both strains advancing age was associated with structural changes in the anterior lobe, including a progressive decrease in the relative number of eosinophils, an increase in the relative number of chromophobes, a decrease in mitotic activity, the appearance and increase in number of vacuolated basophils, the appearance and increase of colloid degeneration of anterior lobe cells and of intercellular colloid, and adenomatous changes. With the exception of the latter, these changes appeared earlier and were more intense in the Albany rats. In the ovaries advancing age was associated with a progressive decrease in the numbers of normal follicles, total follicles (normal plus atretic), and corpora lutea. A partial failure of ovulation and an increased follicular atresia occurred. Interstitial tissue became more abundant and wheel cells appeared and became more numerous. The alterations occurred earlier and were more pronounced in the Albany rats.—Authors' abstract.

Studies on Prostatic Cancer. V. Excretion of 17-Ketosteroids, Estrogens and Gonadotropins before and after Castration. Scott, W. W., and Vermeulen, C. [*Univ. of Chicago, Chicago, Ill.*] J. CLIN. ENDOCRINOL., **2**:450-456. 1942.

In a group of 10 patients with prostatic carcinoma and roentgenographic evidence of skeletal metastases, the average value of urinary 17-ketosteroids (in 6 day samples) before operation was 7.6 mgm. per 24 hours. The range

was 3.6 to 11.7 mgm. After castration the values were less; the lowest were observed 2 to 14 days after operation, at an average of 6.5 days. The role played by operative procedures in these lowered titers could not be identified. The postoperative fall in values was not sustained Levels of these steroids returned after castration to a point higher than they had been previous to operation; per 24 hours the range was 7.3 to 24.4 mgm., the average 11.4 mgm. Ten other patients, studied only subsequent to bilateral orchiectomy carried out as a therapeutic measure for prostatic cancer, had values with a range of 1.8 to 18.2 mgm. per 24 hours, and an average of 6.6 mgm. Beta forms, which represented about 10% of the total amount of 17-ketosteroids prior to castration, did not account for the rise in values after operation.

Preoperatively, the titers of urinary estrogens were 12 to 13 I.U. per 24 hours. In 4 of 6 patients studied the amounts were reduced after operation.

The quantities of urinary gonadotropins were increased after castration, but the amounts were considered to be less than those observed in younger eunuchs.—J. B. H.

Absorption of Subcutaneously Implanted Pellets of Diethylstilbestrol in Men. Shimkin, M. B., and Zon, L. [*Marine Hosp., Baltimore, Md.*] J. Nat. Cancer Inst., **3**:367-370. 1943.

In the effort to find a more convenient method of administering stilbestrol than by daily oral doses, pellets of diethylstilbestrol were implanted subcutaneously in 9 male patients, and were removed and weighed after varying periods. The pellets were cylindrical in shape, weighed 50 mgm., and were prepared either by compression or by fusion. It was found that such pellets were absorbed at a rate of 0.35 to 0.45 mgm. per day for at least 100 days. Clinical evidence of the efficacy of this method of administration was found in the development of gynecomastia and, in one patient with prostatic cancer, in a drop in the serum acid phosphatase.—H. Q. W.

Gonadectomy and Adrenal Neoplasms. Woolley, G. W., Fekete, E., and Little, C. C. [*Jackson Mem. Lab., Bar Harbor, Maine*] Science, **97**:291. 1943.

When mice of the extreme dilution strain (ce) were gonadectomized at 2 days of age, carcinoma of the adrenal cortex occurred, its frequency increasing with age up to 1 year when it reached 100%. No such tumors have so far been observed in normal male and female mice of the ce strain. This observation is linked with the theory that hormonal imbalance may be one of the factors leading to this and other types of cancer.—M. B.

Estrogenic Hormones in the Genesis of Tumors and Cancers. Allen, E. [*Yale Univ. Sch. of Med., New Haven, Conn.*] Endocrinology, **30**:942-952. 1942.

This paper gives a short review of tumors and cancers occurring in experimental animals after long-continued treatment with estrogenic hormones. Genital organs are involved primarily, but nongenital tissues also are affected. The uterus may develop cancer of the cervix (in mice) or fibromyomas of the cornua (in guinea pigs). The mammary glands are especially susceptible to cancer. In certain inbred strains of mice, low tumor incidence among females is increased by estrogenic treatment. Males of strains in which the females are susceptible to spontaneous mammary cancer may have the disease after injections of estrogen. The testes of mice respond to this estrogenic treatment by hypertrophy of the interstitial cells. In the A strain, unilateral nodules may become large tumors. These are transplantable into other mice of this strain if estrogen is injected into the hosts. The tumor tissue may secrete androgenic hormone. Pituitary hypertrophy and chromophobic tumors of considerable size can be induced in high incidences in mice of certain strains and in rats. The suprarenal cortex may develop tumors after long estrogenic treatment in mice. Mice ovariectomized at early ages resumed estrous cycles late in life. Cortical tumors found at autopsy are considered responsible for the secretion of estrogen in these cases. Growth of new bone in the marrow cavities of mice and several species of birds may be induced by estrogenic hormone. Osteogenic tumors have been reported in albino mice. Several hyperplastic or hypertrophic conditions, definitely atypical, have followed excessive estrogenic stimulation. These include cystic hyperplasia of the uterus, metaplastic changes of male accessory organs, leukemia (lymphatic), and hypertrophy of the bile ducts. Cystic ovaries may be induced by unbalanced pituitary stimulation. In these cases hypertrophic uterine conditions are induced by endogenous estrogen. From these experiments endocrine secretions appear as important factors in the genesis of some atypical growths, including certain tumors and cancers.—C. A. P.

Neoplastic Disease of the Pancreas of Snakes (Serpentes). Ratcliffe, H. L. [*Univ. of Pennsylvania, Philadelphia, Pa.*] Am. J. Path., **19**:359-369. 1943.

The acinar tissue of the pancreas in many species of snakes undergoes unexplained focal necrosis followed by abortive regenerative growth, apparently of the terminal ducts, producing small, edematous, adenoma-like structures. These areas presumably enlarge, and with their enlargement, leukocytes infiltrate the organ, fibrous tissue is increased, and there is further degeneration of acinar and islet epithelium, until occasionally the whole organ is replaced by tissue that has the histologic characters of carcinoma. Among 136 snakes of five families of the order Serpentes, all of which died in captivity, 45 presented some stage in the development of this disease. But of 261 snakes of species that seemed most susceptible to the disease, killed for examination 60 to 90 days after capture, only 10 had developed lesions of this sort, and none presented the more advanced stages of the disease.

Metastases were not found, and local extension occurred infrequently. Transplantation was not attempted.—J. G. K.

Present Status of Research in Cancer. Voegtlin, C. [*Nat. Cancer Inst., Bethesda, Md.*] Am. J. Pub. Health, **32**: 1018-1020. 1942.

A general discussion.—A. C.

Clinical and Pathological Reports

Cancer. Nathanson, I. T. [*Harvard Med. Sch., Boston, Mass.*] NEW ENGLAND J. MED., **227**:830-839. 1942.

A review written especially for the practicing physician. Etiologic factors are considered under the headings of precancerous lesions, diet, and physical and chemical agents, especially carcinogenic chemicals and hormones. Genetic studies, heterologous transplantation of human tumors, viruses, and immunity are also dealt with briefly. The discussion of clinical factors is limited largely to carcinoma of the stomach. The role of hormones is considered from the therapeutic as well as etiologic standpoint. Methods of therapy receive a less complete review since the use of x-rays, radium, and radioactive isotopes is covered in other articles in the same series. There are 94 references to recent literature.—C. W.

HEREDITY

A Cancer Family Manifesting Multiple Occurrences of Bilateral Carcinoma of the Breast. Wood, D. A., and Darling, H. H. [*Stanford Univ. Sch. of Med., San Francisco, Calif.*] CANCER RESEARCH, **3**:509-514. 1943.

A cancer family with data for four generations shows the occurrence of bilateral carcinoma of the breast in a number of instances. Attention was drawn to this interesting family while members of the third generation (three sisters) were being studied. Bilateral mammary cancer, as well as other types, had occurred on both maternal and paternal sides. Two of the three sisters have developed bilateral breast cancer. Thus far the third sister has only one breast involved. One female of the fourth generation developed carcinoma of the breast at the age of 18 years. The question arises what advice, if any, should be given to other female siblings of the fourth generation.—Authors' abstract.

THERAPY—GENERAL

Evaluation of Regional Lymph-Node Dissection in the Treatment of Carcinoma. Taylor, G. W. [*Harvard Med. Sch. and Massachusetts Gen. Hosp., Boston, Mass.*] NEW ENGLAND J. MED., **226**:367-371. 1942.

A review of results in over 5,000 cases. The decision to carry out regional lymph node dissection depends on the presence, or likelihood of development, of metastases. The extent of dissection depends on the known behavior of the cancer and the anatomy of the lymphatic drainage areas. Prophylactic dissections may be performed in extensive carcinomas of high malignancy, but dissection may be deferred when there is little likelihood of metastasis. Dissection is capable of curing metastases in a considerable number of cases, with a postoperative mortality rate that should not be excessively high (from 1 to 9% depending on the area involved).—C. W.

RADIATION—DIAGNOSIS AND THERAPY

Spheno-Occipital Chordoma of Unusual Radiosensitivity. Andrews, J. R. [*Cleveland, Ohio*] RADIOLOGY, **39**:478-479. 1942.

X-rays of the skull of a 71 year old white man with headache and unilateral blindness showed symmetrical destruction of the pituitary fossa, the roof of the sphenoid sinus, and adjacent bone. One month after receiving 1,300 r of roentgen therapy the symptoms were greatly relieved. One year later the nasopharynx was almost completely obstructed with tumor, which again responded dramatically to 1,750 r of radiation. Biopsy from the nasopharynx showed chordoma. A good photomicrograph of this rare tumor is reproduced.—C. E. D.

Irradiation Therapy in the Treatment of Non-Malignant Uterine Bleeding. Barr, R. E. [*Beaumont, Tex.*] TEXAS STATE J. MED., **38**:555-557. 1943.

In addition to the use of irradiation to control abnormal uterine bleeding of endocrine origin, the author discusses irradiation in selected patients with fibromyomas. Young women with small fibroids can be given substerilization doses of roentgen rays to the ovary with satisfactory results. In women over 40, intrauterine implantation of radium and roentgen sterilization are indicated. In young women with large masses, surgery is necessary to avoid the complete sterilization required to control the more extensive hemorrhage. Irradiation of the ovary likewise gives satisfactory results in patients with endometriosis. While full sterilization doses are frequently required in the latter cases, they may be administered without too much hesitancy, as pregnancy in women with this condition is unusual.—M. J. E.

Radiation Therapy in Extensive Bladder Carcinoma. Costlow, W. E. [*Los Angeles Tumor Inst., Los Angeles, Calif.*] CALIFORNIA & WEST. MED., **56**:247-248. 1942.

Thirty-three cases of urinary bladder carcinoma classified as inoperable were treated by supervoltage x-irradiation with or without electrocoagulation. The best results occurred in the group of patients who received the combined therapy.—W. A. B.

Radiation Therapy of Uterine Cancer. Crockett, R. H. [*San Antonio, Tex.*] TEXAS STATE J. MED., **38**:444-448. 1942.

General problems and methods of treatment are discussed.—M. J. E.

Problems in Roentgen Therapy for Hodgkin's Disease and Lymphosarcoma. Desjardins, A. U. [*Mayo Clinic, Rochester, Minn.*] RADIOLOGY, **39**:16-26. 1942.

Radiation therapy in Hodgkin's disease and lymphosarcoma is often administered in a fashion that fails to give the maximum benefit. The author has treated over 2,000 cases and summarizes his experience in the form of several general rules and certain specific directions for treating various parts of the body. In general, therapy is palliative and should be given in limited doses over a brief period of time and only to the lesions causing symptoms, thus preserving normal tissue tolerance for subsequent treatments. In rare instances massive doses are warranted in an attempt to cure localized disease. If possible the ovaries should be spared in women under 40. Rays generated at 140 kv. are usually as effective as more penetrating radiation, and protracted fractional treatments are less effective than 500 to 600 r given within a few days to each field. The general condition

of the patient must be followed carefully during treatment, and daily blood counts are advised particularly when abdominal portals are being used. Radiation leukopenias may persist from 2 weeks to several months and are sometimes permanent. A progressive fall in the red count is a poor prognostic sign and is generally found in the terminal radioresistant phase of the disease.—C. E. D.

End Results in Carcinoma of the Cervix and Uterus Treated with Radium. Dudgeon, H., Jr. [*Waco, Tex.*] Texas State J. Med., **38**:599-602. 1943.

Radium alone (2,400 to 3,000 mgm. hrs., repeated within 6 months if a recurrence develops) is advocated as the treatment of choice for cancer of the cervix, radium plus hysterectomy for carcinoma of the fundus. Of 57 patients with cervical neoplasms treated as indicated, on whom an estimation of a result was possible, 21 remained tumor-free after 5 years; of 15 with cancer of the body, 7 appeared cured.—M. J. E.

Carcinoma of the Cervix Treated by Intravaginal and Rotation Therapy. Faust, J. J. [*Tyler, Tex.*] Texas State J. Med., **38**:602-605. 1943.

In preference to the use of the conventional cross-fire method of irradiation, the author believes more satisfactory results can be obtained by rotation of the patient in the beam of roentgen rays. This method avoids too large a dose to restricted areas of the skin and the deeper normal tissues, while permitting full depth doses to the tumor area. This technic is combined with intravaginal irradiation directed through a suitable speculum. The early beneficial effects of this therapy in 3 cases are discussed, but the final results are as yet not known.—M. J. E.

The Irradiation Treatment of Carcinoma of the Female Genitalia. Fricke, R. E. [*Mayo Clinic, Rochester, Minn.*] Proc. Mayo Clinic, **16**:93-94. 1941.

The radium and roentgen treatment of carcinoma of the ovaries, fallopian tubes, uterine fundus and cervix, vaginal walls, and vulva are considered in this paper. Irradiation therapy is a definite adjunct to surgical measures in the treatment of carcinoma of practically all these organs and some excellent results are obtained by radium therapy alone. In other cases it is a valuable preoperative and postoperative procedure.—J. L. M.

Embryonal Cell Carcinoma of the Testis with Pulmonary Metastases: Three and a Half Year Survival Following Radiation Treatment. Hare, H. F. [*Lahey Clinic, Boston, Mass.*] Lahey Clinic Bull., **3**:16-20. 1942.

A 40 year old man, with widespread pulmonary and lymph node metastasis following orchiectomy for embryonal cell carcinoma, was given roentgen therapy to a total dose of 16,000 r delivered to various portals covering the entire trunk. A severe leukopenic anemia resulted but gradually ameliorated, and the patient was living without evidence of disease 3 years later.—C. E. D.

A Case of Carcinoma of the Duodenal Bulb Diagnosed Preoperatively. Hartzell, H. V. [*King County Hosp., Seattle, Wash.*] Radiology, **39**:474-477. 1942.

A palpable mass in the abdomen of a 69 year old white woman was diagnosed roentgenologically as "suspicious of a primary neoplasm of the duodenum" because of the presence of a constant filling defect and irregular mucosal pattern. The suspicion was confirmed at autopsy 2 weeks after exploratory laparotomy.—C. E. D.

Radiation in Cancer of the Corpus Uteri. Kaplan, I. I. [*Bellevue Hosp., New York, N. Y.*] Radiology, **39**:135-143. 1942.

Radiation is generally accepted as superior to surgery in the treatment of carcinoma of the cervix. The diverse opinions on the proper treatment of carcinoma of the fundus are reviewed, and some of the appliances and technics used in intracavity radium therapy are described and illustrated.

The author used roentgen rays, radium, or combinations of the two, in the treatment of 95 patients with malignant tumors of the body of the uterus. Seventy-four patients had adenocarcinoma, 11 carcinoma of undetermined type, 6 epithelioma, and 4 sarcoma. Irradiation was postoperative in 34 cases, preoperative in 16, and used alone in 45. Most of the uteri removed after radiation contained no residual carcinoma. Of the 34 patients known to be dead, 23 died within a year. The 35 living patients have survived from 1 to 14 years.

Properly administered radiation gives as good results as surgery in cancer of the body of the uterus; intrauterine radium applications are safe and often simplify subsequent operations; palliative irradiation is definitely beneficial.—C. E. D.

Further Experiences in the Treatment of Lymphosarcoma with Radioactive Phosphorus. Kenney, J. M., and Craver, L. F. [*Memorial Hosp., New York, N. Y.*] Radiology, **39**:598-607. 1942.

Lymphosarcoma is usually a systemic disease, and some form of systemic therapy is theoretically preferable to local irradiation. Lymph nodes invaded by lymphosarcoma absorb about 3.5 times as great a concentration of radioactive phosphorus as do the tissues of the body in general and are hence subjected to selective irradiation.

Twenty-two unselected patients with lymphosarcoma were treated with radioactive phosphorus, and 8 brief summaries of 8 cases are given. Ten patients are living, and 4 of these have had complete remissions without recurrence for periods of 3 to 12 months. Success or failure appeared to depend on two factors: the differential absorption of radioactive phosphorus in the diseased tissues and the radiosensitivity of the tumor cells. Serious depression of blood counts was seldom encountered. It is believed that radioactive phosphorus should be used primarily or as an adjunct to x-ray in practically all cases of lymphosarcoma.—C. E. D.

Irradiation Treatment of Cavernous Hemangioma with Special Reference to So-Called Contact Roentgen Irradiation. Kerr, H. D. [*State Univ. of Iowa, Iowa City, Iowa*] Radiology, **39**:383-388. 1942.

Lesions about the head and neck made up 50% of 177 lesions in 145 consecutive cases of cavernous hemangioma involving the skin and subcutaneous tissues. Eighty-six per cent of the patients were less than 1 year old, and girls outnumbered boys roughly 3 to 1. One series of 96 cases treated with radium gave 63.5% good results. Another series of 49 cases treated by Chaoul "contact"

roentgen radiation gave 69% good results. Two case histories are reported, and 7 photographs reproduced.

Although the two methods gave comparable end results, the author prefers roentgen therapy because of the shorter treatment time and greater convenience of administration.—C. E. D.

The Therapeutic Use of Artificially Produced Radioactive Substances. Radiophosphorus, Radiostrontium, Radiodine, with Special Reference to Leukemia and Allied Diseases. Low-Beer, B. V. A., Lawrence, J. H., and Stone, R. S. [*Univ. of California, Berkeley, Calif.*] Radiology, **39**:573-597. 1942.

Since radioactive elements are the same, chemically and metabolically, as their inactive isotopes, and since they emit radiation comparable in action to some of the radiations from radium, they may be used for the therapeutic administration of internal radiation. Particular elements are chosen for their ability to localize selectively in special tissues. Radiophosphorus shows some degree of localization in rapidly growing tissue and has been used with some success in the treatment of leukemia and related disorders. A chart is presented of the survival of 212 patients treated with this method at the Crocker Radiation Laboratory since 1937. The 90 patients still alive are chiefly those treated in recent years. Fairly good results have been obtained in chronic myelogenous and lymphatic leukemia, lymphosarcoma, and polycythemia. Patients with Hodgkin's disease, multiple myeloma, or carcinoma were seldom benefited. A number of case histories are given, and the methods of administration are described with the aid of charts. Results superior to those obtained with external radiation are not claimed, but the new method has promise. Treatment of bone tumors with radioactive strontium, and of thyroid tumors with radioactive iodine, is still in the experimental phase.—C. E. D.

Roentgen Treatment of Inoperable Ulcerating Carcinoma of the Breast. MacCarty, W. C., Jr., and Leddy, E. T. [*Mayo Clinic, Rochester, Minn.*] Radiology, **39**: 711-714. 1942.

Ninety-eight patients suffering from inoperable ulcerating carcinoma of the breast were treated in the Section on Therapeutic Radiology of the Mayo Clinic from 1925 to 1940. The average time elapsed from the onset of the disease was 26 months, and the average age 55 years. Only 2 patients were free of metastases. Roentgen therapy was administered in converging beams centered on the tumor and delivered to 4 or 6 portals covering the anterior chest wall on the affected side. Supplementary axillary and supraclavicular portals were used as the case required. A single dose of 500 to 600 r was given to each portal, and the series repeated in a month and again after another month. At the conclusion of this study, 43 patients were dead, 24 were not available for further observation, 24 were living and stated that they were improved, and 7 were worse after treatment. In 23 patients the ulceration healed completely, and in an equal number its size was reduced. Considering the hopeless condition of the patients, the palliative results were regarded as good.—C. E. D.

Argentaffin Tumors of the Small Bowel: A Roentgen Sign of Malignant Change. Miller, E. R., and Herrmann, W. W. [*Univ. of California Med. Sch., San Francisco, Calif.*] Radiology, **39**:214-220. 1942.

Gaseous distention of the small bowel, with partial obstruction, a tumor, a small filling defect, and kinking at the site of obstruction, are described as a roentgenological complex characteristic of malignant carcinoid. Three cases are reported, one of which was diagnosed preoperatively. Four roentenograms are reproduced and 53 references given.—C. E. D.

A Roentgenologic Aspect of Pseudomyxoma Peritonaei. Pugh, D. G. [*Mayo Clinic, Rochester, Minn.*] Radiology, **39**:320-322. 1942.

A case of pseudomyxoma peritonaei is presented in which a roentgenogram of the abdomen showed many annular, calcified structures, presumably the calcified walls of pseudomucinous cysts, and in addition, many soft tissue masses. A second case showing a similar picture was probably pseudomyxoma but might have been paraffinoma. In 3 other patients with pseudomyxoma peritonaei, films of the abdomen did not show similar calcifications.—C. E. D.

Results of Irradiated Treatment of Cancer of the Lip: Analysis of 636 Cases from 1926-1936. Schreiner, B. F., and Christy, C. J. [*State Inst. for Study of Malignant Diseases, Buffalo, N. Y.*] Radiology, **39**:293-297. 1942.

A study was made of 636 consecutive, histologically verified, squamous cell carcinomas of the lip treated by radiation. Tables are presented to show the age incidence of the patients, and the extent and size of the initial lesions. Lip cancer was 38 times as common in men as in women and occurred 29 times as frequently on the lower as on the upper lip. Multiple primary lesions were present in 12 patients. Thirty-two per cent of the patients were engaged in occupations exposing them to the weather, and 87% used tobacco.

Treatment by roentgen rays and radium is, in general, as effective as surgery in curing the disease and gives better cosmetic results. In the authors' series the 5 year absolute cure rate was 58.9%, and the rate rose to 74.4% when patients were excluded who were lost from observation or died of intercurrent disease. Only 2 of 38 patients with proved metastatic lesions survived 5 years.—C. E. D.

Effect of Combined Fever and X-Ray Therapy on Far-Advanced Malignant Growths. Shoulders, H. S., Turner, E. L., Scott, L. D., and Grant, W. H. [*Meharry Med. Coll., Nashville, Tenn.*] Radiology, **39**:184-193. 1942.

The literature on combined heat and radiation treatment of tumors is reviewed. This method of treatment was used by the authors for 42 patients with a variety of advanced, inoperable malignant tumors. The temperature of the patient was maintained at 104–106° F. in a fever cabinet for 30 to 60 minutes. This was followed immediately by 200 kv. roentgen therapy directed to the site of the tumor. A tabular summary gives the details of treatment and the results for each patient. Five case histories are given in greater detail. Symptomatic improvement was obtained in 65% of the 42 cases. Cures are not claimed, but the results seemed more favorable than could have been expected from radiation alone.—C. E. D.

Radium Poisoning. Stevens, R. H. [*Detroit, Mich.*] Radiology, **39**:39-47. 1942.

A case of radium poisoning is presented and discussed at length. The patient, a 36 year old man, was given intravenous injections of radium chloride to a total dose of 440 μgm., between January, 1925, and November, 1930, as treatment for Hodgkin's disease. In the subsequent years the patient developed extensive radium necroses of the mandible and of the vertebrae, but the Hodgkin's disease was controlled. Eighteen years after the first injection the patient was working and in fairly good health even though his body still contained 11.4 μgm. of radium, an amount in excess of the accepted lethal dose.—C. E. D.

The Treatment of Cancer with Fast Neutrons. Stone, R. S., and Larkin, J. C., Jr. [*Univ. of California Med. Sch., Berkeley Calif.*] Radiology, **39**:608-620. 1942.

Doses of fast neutrons produced by the cyclotron may be measured with the same ionization chamber as that employed for x-rays. Since the physical factors are different, the resulting unit is called "n" (neutron unit) rather than "r" (roentgen). The skin of normal subjects was exposed to a beam of neutrons and showed a minimal erythema after doses of 110 n. The dose of 200 kv. x-rays necessary to produce this effect is about 650 r. Hence 1 n is equivalent to about 6 r.

Between December, 1939, and September, 1941, 120 patients with cancer in various locations underwent a series of exposures to neutron radiation. Almost all these patients were considered incurable by surgery or ordinary radiation. They were given fractional exposures of 7.8 to 55 n per day and total field doses of 275 to 1165 n. The technic of treatment is described. Local and systemic reactions were quite severe in heavily treated subjects, but no patient died during treatment and only 8 during the subsequent 3 months. Complete regression of the tumor in the field of treatment occurred in 26 patients and partial regression in 53. Since the maximum period of observation has been 20 months, cures cannot be discussed. A total of 61 of the group have died. In 14 of 31 autopsies there was no gross or microscopic evidence of cancer in the treated area.—C. E. D.

The Roentgenographic Appearance of the Bones in Cushing's Syndrome. Sussman, M. L., and Copleman, B. [*Mt. Sinai Hosp., New York, N. Y.*] Radiology, **39**:288-292. 1942.

Seven women with adrenal tumors (4 carcinomas and 3 adenomas) presented the clinical features of Cushing's syndrome. The bones were studied roentgenologically, and osteoporosis was found in 6 of the patients. The bone changes were most frequent in the skull, involving principally the frontal and parietal bones. Diffuse osteoporosis of the vertebral bodies was common and in one advanced case was associated with multiple compression fractures. An almost pathognomonic finding was a symmetrical calcified enlargement of the lower ribs in the region just proximal to the costochondral junction. These enlargements suggested callus although no fracture lines were demonstrated. Four roentgenograms are presented.—C. E. D.

Altered Behavior Caused by Removable Tumor of the Brain: Site Suggested by the Electro-Encephalogram. Woltman, H. W., and Craig, W. McK. [*Mayo Clinic, Rochester, Minn.*] Proc. Mayo Clinic, **16**:49-51. 1941.

Electroencephalography is a clinical test only and as such its results must be correlated with other findings before the complete picture emerges and the diagnosis can be made. Although electroencephalography does not tell us the nature of a lesion, nor its exact site, it is an aid to cerebral localization. In the case reported it led the authors to advise encephalography and ventriculography in their search for a focal rather than for a diffuse disease of the brain.—J. L. M.

Skin and Subcutaneous Tissues

Precancerous Dermatoses. Ormsby, O. S. [*Rush Med. Coll., Univ. of Chicago, Chicago, Ill.*] New England J. Med., **224**:793-798. 1941.

A review from a clinical and pathological standpoint.—G. H. H.

Tumors of Sebaceous Glands. Warren, S., and Warvi, W. N. [*New England Deaconess Hosp., Boston, Mass.*] Am. J. Path., **19**:441-459. 1943.

A detailed discussion and review of the literature on benign and malignant tumors of sebaceous glands. The authors point out that most so called adenomas are instances of hypertrophy or hyperplasia of sebaceous glands, true sebaceous adenomas being rare. They record brief notes on 5 adenomas, none of which was diagnosed clinically.

Twenty-nine cases of sebaceous gland carcinoma are reported in tabular form and discussed. Many of the carcinomas of this sort probably arise from benign growths; they often resist treatment and not infrequently metastasize. The pathologic entity is distinguished from basal cell or epidermoid carcinoma.—J. G. K.

Nervous System

Meningeal Gliomatosis Secondary to Intramedullary Glioma. Amyot, R. [*Hôpital Notre Dame, Montreal, Canada*] Arch. Neurol. & Psychiat., **49**:383-397. 1943.

Report of a case of meningeal gliomatosis originating from an intramedullary glioma. The tumor was notable for its extension to the leptomeninges and even to the dura which was destroyed locally. For this type of tumor, the author proposes the descriptive name of "malignant glioblastoma with astrocytic evolution."—A. C.

Intracranial Epidermoids Occurring Simultaneously below and above the Tentorium. Black, H. A. [*Brooklyn Hosp., Brooklyn, N. Y.*] Arch. Neurol. & Psychiat., **49**:213-222. 1943.

Of 205 epidermoids located within the cranial cavity, as described in the literature, 7 were situated in both supratentorial and infratentorial positions. The paper concerns an additional case in which the lesion involved both compartments. It is suggested that the term "cutaneous proliferating cyst," introduced by Paget, is an acceptable designation for the neoplasms now called epidermoid, or cholesteatoma.—A. C.

Tumors in the Region of the Cauda Equina. A Review of Twenty-Five Cases. Cohen, I., and Kaplan, A.

[Mt. Sinai and Montefiore Hosps., New York, N. Y., and U. S. Naval Hosp., Portsmouth, Va.] Am. J. Surg., **60**:36-43. 1943.

A study of 25 cases.—W. A. B.

Schwannomas (Neurilemmomas) in the Head and Neck. Ehrlich, H. E., and Martin, H. *[Memorial Hosp., New York, N. Y.]* Surg., Gynec. & Obst., **76**:577-583. 1943.

Twelve cases of schwannoma in the tissues about the head and neck are described, 3 tumors originating from the phrenic nerve. The growths were clinically and anatomically benign; they proved radioresistant, but none recurred following excision.—J. G. K.

Extensive Angiomatous Formations on Left Fronto-Parietal Cortex. Hilliard, T. L. Proc. Roy. Soc. Med., **36**:37-38. 1942.

A case report.—E. L. K.

Calcification of the Cerebral Cortex Associated with a Meningotheliomatous Meningioma. Pathologic Study, with Comment on Incomplete Types of the Neurocutaneous Syndrome. Lichtenstein, B. W., and Lev, M. *[Univ. of Illinois, Chicago, Ill.]* Arch. Neurol. & Psychiat., **49**:507-517. 1943.

The paper appears to be the first in which cortical calcification is reported in association with a meningotheliomatous meningioma. The clinical diagnosis of Alzheimer's disease was complicated by bilateral primary optic nerve atrophy resulting from pressure of the meningioma on the optic nerves and chiasma.—A. C.

Neurofibroma of Cervical Spinal Cord (Partial Removal). Macnab, G. H. Proc. Roy. Soc. Med., **36**:35. 1942.

A case report.—E. L. K.

Intracranial Dermoid and Epidermoid Tumors. Martin, J., and Davis, L. *[Northwestern Univ. Med. Sch., Chicago, Ill.]* Arch. Neurol. & Psychiat., **49**:56-70. 1943.

A report of 1 intracranial epidermoid and 4 dermoid tumors. In all 5 cases, surgical removal of the tumor was successful.—A. C.

Polyuria and Brain Tumor. Maurer, L. E., and Neff, F. C. *[Sch. of Med., Univ. of Kansas, Kansas City, Kans.]* J. Kansas M. Soc., **43**:259-260. 1942.

A case report.—C. W.

Angioma of the Cerebral Cortex. Meadows, S. P. Proc. Roy. Soc. Med., **36**:36. 1942.

A case report.—E. L. K.

Calcified Intracranial Tumour. Meadows, S. P. Proc. Roy. Soc. Med., **36**:36-37. 1942.

A case report.—E. L. K.

Midbrain Deafness. Tumor of the Midbrain Producing Sudden Complete Deafness. Sloane, P., Persky, A., and Saltzman, M. *[Mt. Sinai Hosp., Philadelphia, Pa.]* Arch. Neurol. & Psychiat., **49**:237-243. 1943.

The present case of sudden and complete deafness was caused by the presence of a glioma infiltrating the tegmentum of the midbrain. Milder symptoms resulted from involvement of the hypothalamus.—A. C.

Malignant Meningiomas. A Clinical and Pathological Study. Turner, O. A., Craig, W. McK., and Kernohan, J. W. *[Mayo Clinic, Rochester, Minn.]* Surgery, **11**:81-100. 1942.

A general review.—W. A. B.

Vascular Malformations and Vascular Tumors Involving the Spinal Cord. A Pathologic Study of Forty-Six Cases. Turner, O. A., and Kernohan, J. W. *[Mayo Clinic, Rochester, Minn.]* Arch. Neurol. & Psychiat., **46**:444-463. 1941.

A classification of vascular malformations and vascular tumors of the spinal cord, based on the study of 46 cases, is proposed. Malformations include telangiectasis and angiomas, and tumors are divided into capillary, cavernous, and sarcomatous neoplasms.—A. C.

Ear

Granular Cell Myoblastoma. Horn, R. C., Jr., and Stout, A. P. *[Presbyterian Hosp., New York, N. Y.]* Surg., Gynec. & Obst., **76**:315-318. 1943.

Two cases of granular cell myoblastoma of the external auditory canal are added to the 30 cases of this type of neoplasm reported as occurring at various body sites. Some of these tumors are highly vascular and have an organoid arrangement that may give them a resemblance to neoplasms of endocrine gland origin.—H. G. W.

Breast

Tumors of the Breast. Bell, E. T. *[Univ. of Minnesota, Minneapolis, Minn.]* Texas State J. Med., **38**:537-538. 1943.

Included in this short paper is a discussion of cystic disease of the breast, which is not considered by the author to be a precancerous condition. In the differential diagnosis of benign and malignant lesions the importance of a simple, but frequently overlooked, procedure of palpation of the breast with the flat hand is stressed. Only in this way can the relationship of a mass to the mammary tissue be established. Intraductal papilloma, believed by many observers to be potentially malignant, is classified as a benign lesion requiring conservative surgery and not more extensive resection. In a series of 714 mammary carcinomas, 90% were classified as the scirrhus type.—M. J. E.

Cystic Disease of the Breast. A Critical Review. Davis, H. H. *[Omaha, Neb.]* Surgery, **10**:663-674. 1941.

Cystic disease of the breast is considered to be of two types: the cystic type with fairly large cysts of the blue-domed variety, lined with thin epithelium; and the adenocystic type with many small cysts, lined with hyperplastic epithelium. Carcinoma rarely develops in the former type but occurs more frequently in the latter. Cystic disease may arise as a result of overactivity of the anterior pituitary gland, associated with deficient inhibition by the ovaries.—W. A. B.

Myoepithelial Proliferations in the Human Breast. Kuzma, J. F. *[Marquette Univ. Sch. of Med., Milwaukee, Wis.]* Am. J. Path., **19**:473-489. 1943.

The myoepithelial cells of the breast are described. These are smooth muscle cells, epithelial in origin, arranged about the ducts and situated on the "epithelial" side of the basement membrane; they stain distinctively with Van Gieson's and Masson's stains. The myoepithelial cells manifest the ability to proliferate, either alone or in conjunction with the epithelium, especially in breasts showing mastopathia cystica and fibroadenomatosis, and

they survive and proliferate in senile involution and fibrosis of the breast. Myoepithelial proliferations may be confused with true malignant changes, hence suspicious breast lesions should be carefully studied, and if the proliferations are found to be myoepithelial the lesions should be considered benign. There are 10 figures.—J. G. K.

Bilateral Giant Fibroadenoma Simulating Malignancy in Pregnancy. Reed, H. L., and Hiebert, A. E. [*St. Francis Hosp. and Sedgwick County Hosp., Wichita, Kans.*] J. Kansas M. Soc., **43**:284-287. 1942.

A case report.—C. W.

Carcinoma of the Breast. Stabins, S. J., and Dowdy, A. H. [*Sch. of Med. and Dentistry, Univ. of Rochester, Rochester, N. Y.*] Surgery, **11**:898-905. 1942.

An analysis of 193 cases of carcinoma of the breast.—W. A. B.

Female Genital Tract

Pseudomucinous Cystadenoma. Calkins, L. A., and True, O. H. [*Kansas City and Hays, Kans.*] J. Kansas M. Soc., **42**:255 and 264. 1941.

A case report illustrating the possibility of malignancy in a secondary implant even though the primary tumor is microscopically benign.—C. W.

Newer Ovarian Neoplasms. Dockerty, M. B. [*Mayo Clinic, Rochester, Minn.*] Proc. Mayo Clinic, **16**:91-92. 1941.

The essential data obtained from a study of 75 examples of "newer" types of ovarian neoplasms are presented in tabular form. The following items are considered: histogenesis, age of patients, characteristic symptoms or syndrome, unilateral or bilateral occurrence of the tumor, gross appearance, microscopic pattern, 5 year survival of patients, and the hormone elaborated. Under the newer types are classed: granulosa cell tumor, theca cell tumor, arrhenoblastoma, dysgerminoma, and Brenner tumor.—J. L. M.

Theca Cell Tumor of the Ovary. Dowling, U. J. [*Sweetwater, Tex.*] Texas State J. Med., **38**:41-42. 1942.

Surgical removal of a theca cell tumor of the ovary in a woman of 61 years effected a complete cure. After extirpation, the evidence of estrogen secretion by the tumor, such as mammary enlargement and uterine bleeding, promptly began to disappear.—M. J. E.

Mesodermal Mixed Tumors of the Corpus Uteri. Lebowich, R. J., and Ehrlich, H. E. [*Littauer Hosp., Gloversville, N. Y.*] Surgery, **10**:411-433. 1941.

A report of a case and review of the literature.—W. A. B.

Intestinal Obstruction as a Phase of Carcinoma of the Cervix. Pearson, B., and Garcia, M. [*Sch. of Med., Louisiana State Univ., New Orleans, La.*] Surgery, **11**:636-643. 1942.

The incidence of carcinomatous obstruction of the bowel was 12.1% among 74 patients with squamous cell carcinoma of the cervix, coming to autopsy during an 11 year period.—W. A. B.

Male Genital Tract

The Treatment of Cancer of the Prostate with Castration and the Administration of Estrogen. A Preliminary Report. Chute, R., and Willetts, A. T. [*Harvard Med. Sch., Boston, Mass.*] New England J. Med., **227**:863-869. 1942.

A report on the treatment of 37 cases of inoperable carcinoma of the prostate by castration, the use of stilbestrol, or both. The general results were satisfactory, only one patient apparently receiving no benefit. Beneficial effects included rapid and lasting relief of pain; improvement in appetite, weight, and strength; and a feeling of well-being. However, there was no radiographic evidence of arrest or regression of bone metastases. The acid phosphatase level was high in some but not in all cases with metastases; when elevated it fell rapidly after castration and was still further reduced by stilbestrol. The 17-ketosteroids were lowered in most cases after orchiectomy; the level seemed to have no reaction to the course or progress of the disease. The authors recommend "intracapsular orchidectomy" as a means of reducing the psychological effects of castration.—C. W.

Castration for Carcinoma of the Prostate. Report of Forty-One Cases. Neuswanger, C. H., and Vermooten, V. [*Yale Univ. Sch. of Med., New Haven, Conn.*] New England J. Med., **227**:626-627. 1942.

A report on the early postoperative effects of bilateral orchiectomy and transurethral resection on 41 patients with carcinoma of the prostate. Four particularly striking cases are reported in detail. The observations substantially confirm those reported by Huggins.—C. W.

Carcinoma of the Prostate. Quinby, W. C. [*Peter Bent Brigham Hosp., Boston, Mass.*] New England J. Med., **227**:512-515. 1942.

A review of recent advances including clinical, enzymatic, and radiographic studies. The therapeutic use of androgenic substances is discussed, and recommended treatment for various types of cases is outlined.—C. W.

Urinary System—Male and Female

Chemical Carcinogenesis, Drugs, Dyes, Remedies and Cosmetics with Particular Reference to Bladder Tumors. Davis, E. [*Univ. of Nebraska Coll. of Med., Omaha, Neb.*] J. Urol., **49**:14-27. 1943.

The hypothesis is advanced that the underlying cause of recurrent vesical papillomatosis may possibly be chemical in nature, and that the chemical agents may be derived from cosmetics, drugs, and industrial chemicals.—H. G. W.

Tumors of the Urinary Bladder. Hiemstra, W., and Creevy, C. D. [*Univ. of Minnesota, Minneapolis, Minn.*] Radiology, **39**:175-183. 1942.

One hundred and seventy-four cases of bladder tumor were treated at the University of Minnesota Hospitals from 1930 through 1939. These included 28 benign papillomas, 57 papillary carcinomas, and 89 infiltrating carcinomas. There were 142 male and 32 female patients, a ratio of 4.5 to 1. The majority of the patients were between the ages of 50 and 70. Hematuria was the first symptom in 85% of the cases, and the delay in seeking treatment averaged 2.3 years. Surgical and radiation therapy are discussed, and charts and tables are presented to show the distribution of the tumors and the results of various types of treatment. Only 12.8% of the patients with

carcinoma survived 5 years or more. Proper use of radiation may improve these results. Twenty-seven references are cited.—C. E. D.

Oral Cavity and Upper Respiratory Tract

Cancer of the Face and Mouth. Blair, V. P., and Byers, L. T. [*St. Louis, Mo.*] Texas State J. Med., **38**:641-645. 1943.

A general discussion on diagnosis and suggested methods of treatment.—M. J. E.

Panlaryngectomy for Advanced Carcinoma of the Larynx. Brunschwig, A. [*Univ. of Chicago, Chicago, Ill.*] Surg., Gynec. & Obst., **76**:390-394. 1943.

Panlaryngectomy seemed advisable in 5 patients with advanced extrinsic carcinoma of the larynx in whom x-ray treatments had failed to eradicate the growths. The technic of the operation is described. The results were palliative.—J. G. K.

Cancer of the Larynx. Equen, M., Neuffer, F., and Matthews, W. B. [*Atlanta, Ga.*] South. M. J., **36**:321-324. 1943.

A general discussion.—W. A. B.

Pseudo-Adenomatous Basal-Cell Carcinoma of the Tongue (Salivary Gland Tumor). Lampe, I. [*Univ. of Michigan, Ann Arbor, Mich.*] Radiology, **39**:54-61. 1942.

A case is reported of pseudoadenomatous basal cell carcinoma arising in a mixed salivary gland tumor of the base of the tongue. The patient, a white male of 57, was followed for 13 years during which time metastases developed in the cervical lymph nodes, lungs, pelvic bones, and right femur. Radiation therapy resulted in considerable regression of the primary lesion and lymph node metastases, and relieved pain in the osseous metastases. When last heard from, the patient felt well in spite of persistent tumor in the mouth, lungs, and femur. Five roentenograms and 2 photomicrographs are reproduced.—C. E. D.

Salivary Glands

Metastasis of Mixed Tumors of the Salivary Glands. Mulligan, R. M. [*Univ. of Colorado Sch. of Med., Denver, Colo.*] Arch. Path., **35**:357-365. 1943.

In contrast to the rather high recurrence rate, development of metastases from these tumors seems to be relatively rare. The authors add a case to the 20 recorded in the literature.—H. G. W.

Papillary Cystadenoma Lymphomatosum of the Parotid Gland. Robinson, D. W., and Harless, M. S. [*Univ. of Kansas Hosps., Kansas City, Kans.*] Surg., Gynec. & Obst., **76**:449-452. 1943.

Four cases are added to the 67 previously reported in the literature. Three figures illustrate the growths, which were benign and composed of numerous cystic spaces lined with well differentiated pseudostratified columnar epithelium thrown up into broad based papillae. The stroma contained a delicate reticulum, in which were numerous closely packed lymphocytes or follicles with large germinal centers. Only 2 of the previously reported cases had exhibited malignant changes.—J. G. K.

Intrathoracic Tumors—Lungs—Pleura

Recent Progress in the Surgical Treatment of Lung Tumors. Adams, W. E. [*Univ. of Chicago, Chicago, Ill.*] Surgery, **10**:836-853 and 1005-1026. 1941.

A general review.—W. A. B.

Malignant Adenoma of the Lung. Carcinoma-Like Tumors with Long Clinical Course. Adams, W. E., Steiner, P. E., and Bloch, R. G. [*Univ. of Chicago, Chicago, Ill.*] Surgery, **11**:503-526. 1942.

Five cases of endobronchial tumor with malignant manifestations, characterized by a long clinical course.—W. A. B.

Bronchial Adenoma with Metastases to the Liver. Anderson, W. M. [*Washington Univ. Sch. of Med., St. Louis, Mo.*] J. Thoracic Surg., **12**:351-360. 1943.

The autopsy findings in the case described revealed a bronchial tumor that would be regarded as benign from its histologic structure but there was a similar nodule in the liver. Bronchial adenomas are discussed from the standpoint of origin and of relation to carcinoid, mixed tumors of the salivary gland, and cylindromas.—E. E. S.

Primary Carcinoma of the Bronchus Associated with Foreign Body. Blake, J. M. [*Schenectady County Tuberculosis Hosp., Schenectady, N. Y.*] Am. Rev. Tuberc., **47**:109-111. 1943.

A report of a case of carcinoma of the bronchus. In the tumor was found embedded a small metal crucifix presumably aspirated 6 years previously.—H. G. W.

Primary Fibrosarcoma of the Chest Wall Following Thoracic Trauma. Blake, J. M., and Bradford, J. K. [*Schenectady County Tuberculosis Hosp., Schenectady, N. Y.*] J. Thoracic Surg., **12**:368-375. 1943.

A case report.—E. E. S.

Endothelioma of the Pleura: Clinical and Roentgenologic Study of Three Cases. Doub, H. P., and Jones, H. C. [*Henry Ford Hosp., Detroit, Mich.*] Radiology, **39**:27-32. 1942.

Three cases of endothelioma of the pleura were found among 345,000 admissions to the Henry Ford Hospital. The histories and autopsies of these 3 cases are presented together with 5 roentgenograms. The outstanding clinical finding was serosanguinous pleural effusion subsequent to an illness resembling respiratory infection. The characteristic flat and nodular projections on the surface of a thickened pleura are best made visible roentgenographically by withdrawing the pleural fluid and replacing it with air. The tumors probably arise from the endothelial cells of lymph spaces or from pleural lining cells.—C. E. D.

Primary and Metastatic Carcinoma of the Lung Simulating Pulmonary Metastases Alone. Freedman, L. M. J., and Bosse, M. D. [*Western Pennsylvania Hosp., Pittsburgh, Pa.*] Radiology, **39**:479-482. 1942.

A case report.—C. E. D.

Anlagen and Rest Tumors of the Lung Inclusive of "Mixed Tumors" (Womack and Graham). Harris, W. H., and Schattenberg, H. J. [*Tulane Univ. Sch. of Med. and Charity Hosp. of Louisiana, New Orleans, La.*] Am. J. Path., **18**:955-967. 1942.

Four tumors of the lung, manifesting evidences of origin either in anlagen or from more than one germinal layer, are described and illustrated. Two of the growths developed during intrauterine life.—J. G. K.

Cancer of the Lung in Infancy. Hauser, H. [*Sch. of Med., Western Reserve Univ., Cleveland, Ohio*] RADIOLOGY, **39**:33-38. 1942.

A case is reported of a colored female infant who died at the age of 18 months after an illness of 6 months. Autopsy revealed small cell carcinoma of the left lung. The literature is briefly reviewed to show the rarity of this condition in infants and children. Among the lung carcinomas reported in patients under 20 years of age, there is a great preponderance of males over females.—C. E. D.

Carcinoma of the Bronchus. Holmes, G. W. [*Massachusetts Gen. Hosp., Boston, Mass.*] NEW ENGLAND J. MED., **227**:503-508. 1942.

A review of recent literature, with a study of 158 proved cases previously reported and 68 additional cases considered largely from the radiographic standpoint. Diagrammatic charts show the types of tumors and implications with reference to diagnosis and treatment.—C. W.

Bronchial Involvement in Metastatic Pulmonary Malignancy. King, D. S., and Castleman, B. [*Massachusetts Gen. Hosp., Boston, Mass.*] J. THORACIC SURG., **12**:305-315. 1943.

Two patients having hemoptysis and a shadow in the lung simulating that of primary bronchogenic tumor proved to have pulmonary metastases when examined at autopsy. In one patient bronchial obstruction by the secondary tumor was also present. A review of 109 cases of metastatic tumor in the lungs showed that the secondary tumor involved bronchi in 20 cases but was associated with hemoptysis in only 4 cases.—E. E. S.

Mediastinal Sympathogonioma. Sailer, S. [*Coll. of Med., Univ. of Cincinnati, Cincinnati, Ohio*] AM. J. PATH., **19**:101-119. 1943.

Report of a case in a colored female, aged 65. The tumor was situated in the anterior mediastinum beneath the pericardium and probably originated from embryonal sympathetic elements contained in the deep cardiac plexus. It was composed of small cells of striking uniformity, having darkly stained, round, or oval nuclei, and scanty cytoplasm, which was often bipolar or filamentous as revealed by Masson's trichrome stain. Absence of maturation into larger sympathoblastic cells indicated the embryonal character of the tumor. The growth was encapsulated; there were no metastases.

A tabulation is given of some of the salient features of 13 well documented sympathetic tumors occurring in the thorax, as previously reported in the literature.—J. G. K.

Primary Neurogenic Tumors of the Mediastinum. Schaffner, V. D., Smith, R. P., and Taylor, H. E. [*Dalhousie Univ., Halifax, N. S.*] J. THORACIC SURG., **12**:247-258. 1943.

Three cases of benign intrathoracic neurogenic tumors are reported; namely, a neurinofibroma, a ganglioneuroma simplex, and a ganglioneuroma immaturum.—H. G. W.

Multiple Bilateral Pulmonary Adenomatosis in Man. Sims, J. L. [*Univ. of Wisconsin, Madison, Wis.*] ARCH. INT. MED., **71**:403-409. 1943.

A case is described of pulmonary adenomatosis in man, resembling somewhat the disease jagziekte as found in sheep. References are given to previously reported cases, and the questions are discussed whether the two types of lesions are infectious, of virus origin, and neoplastic. Four figures are shown.—J. G. K.

Neuroblastoma of the Mediastinum with Pheochromoblastomatous Elements. Wahl, H. R., and Robinson, D. [*Univ. of Kansas Sch. of Med., Kansas City, Kan.*] ARCH. PATH., **35**:571-578. 1943.

The history and autopsy findings are given of a 4 year old boy with a thoracic tumor composed of a mixture of neurogenous elements. While the primary tumor contained differentiated nerve elements with a preponderance of pheochrome cells, the metastases, which were widespread in bones and viscera, were comprised of undifferentiated cells of neuroblastomatous type. There are 8 figures.—J. G. K.

Bronchogenic Carcinoma: A Resume and Some Newer Concepts. Wallace, W. S., and Jackson H. G. [*Galveston, Tex., and New Haven, Conn.*] TEXAS STATE J. MED., **38**:605-612. 1943.

This is a review and general discussion based upon observations at autopsy of 28 cases of pulmonary cancer.—M. J. E.

GASTROINTESTINAL TRACT

Fibroma of Esophagus. Report of Case. Adams, R. [*Lahey Clinic, Boston, Mass.*] LAHEY CLINIC BULL., **3**:72-81. 1943.

A fibroma of the esophagus, 6 cm. in diameter, was successfully removed by the transthoracic approach. Details of diagnosis and treatment are described and discussed.—C. E. D.

Primary Adenocarcinoma in a Meckel's Diverticulum. Albright, H. L., and Sprague, J. S. [*Boston Univ. Sch. of Med. and Massachusetts Mem. Hosps., Boston, Mass.*] NEW ENGLAND J. MED., **226**:142-146. 1942.

A case report and review of the literature.—C. W.

Cancer of the Ampulla of Vater. Blake, H. S., and Mills, W. M. [*Topeka, Kans.*] J. KANSAS M. SOC., **43**:335-337. 1942.

A case report.—C. W.

The Surgical Treatment of Carcinoma of the Stomach in Aged Individuals. Bowers, R. F. [*Cornell Univ. Med. Coll., New York, N. Y.*] SURGERY, **11**:869-881. 1942.

A report of 9 cases.—W. A. B.

Advances in the Treatment of Carcinoma of the Rectum. Bowing, H. H., and Dixon, C. F. [*Mayo Clinic, Rochester, Minn.*] M. CLIN. NORTH AMERICA, **25**:915-943. 1941.

This review deals with the diagnosis and treatment of carcinoma of the rectum. The symptoms and diagnostic signs vary according to the region involved. Further, the age, physical characteristics, general condition of the patient, and duration of the disease furnish problems in diagnosis, treatment, and prognosis. Electrosurgery or actual cauterization, radium therapy, and roentgen therapy are not competitive measures but are complementary.

Six diagrams are included to illustrate carcinomas of the rectum and their treatment by both conservative and radical radium methods.—J. L. M.

Carcinoma of the Intrapancreatic Portion of the Common Bile Duct. Brunschwig, A., and Clark, D. E. [*Univ. of Chicago, Chicago, Ill.*] SURGERY, **10**:553-562. 1941.

A report of 2 cases.—W. A. B.

Primary Sarcoma of the Stomach. Cameron, A. L., and Breslich, P. J. [*Northwest Clinic, Minot, N. D.*] SURGERY, **9**:916-930. 1941.

Review of 104 cases reported during a 10 year period, with the addition of 2 cases.—W. A. B.

Lipoma of the Stomach Causing Hemorrhage. Report of Case. Cattell, R. B. [*Lahey Clinic, Boston, Mass.*] LAHEY CLINIC BULL., **3**:34-38. 1942.

A lipoma, 6 cm. in diameter, was successfully removed from the wall of the stomach. The only symptom had been gastric hemorrhage.—C. E. D.

Recent Advances in the Surgical Treatment of Carcinoma of the Colon and Rectum. Cattell, R. B., and Sugarbaker, E. D. [*Lahey Clinic, Boston, Mass.*] SURGERY, **11**:644-652. 1942.

A review.—W. A. B.

Primary Lymphosarcoma of the Intestine in a Boy of Seven. Follow-Up of Nine Years. Charache, H. [*Brooklyn Cancer Inst., Brooklyn, N. Y.*] AM. J. SURG., **59**:601. 1943.

The patient is in good health 9 years after the removal of a lymphosarcoma of the ileum that had involved the adjacent lymph nodes. Of the 404 cases of lymphosarcoma of the intestine reported in the literature, 103 were carefully followed. Of the latter number, only 14 patients survived for 5 years.—H. G. W.

Leiomyoma Malignum of the Stomach. Christopher, F., Benjamin, E. L., and Sauer, L. W. [*Northwestern Univ. Med. Sch., Evanston, Ill.*] SURGERY, **10**:381-386. 1941.

A case report.—W. A. B.

Benign Tumors of the Stomach. Dudley, G. S., Miscall, L., and Morse, S. F. [*Bellevue Hosp., New York, N. Y.*] REV. GASTROENTEROL., **10**:31-44. 1943.

Of the benign gastric tumors studied 76 were found at autopsy and 34 at operation. Of 39 polyps found at autopsy 9 (23%) showed malignant changes, so that gastric resection is probably indicated in this group of tumors.—H. G. W.

Multiple Argentaffinomas in Ileum with Metastasis in Lymph Nodes and in the Liver. Gold, I. R., and Grayzel, D. M. [*Jewish Hosp., Brooklyn, N. Y.*] AM. J. SURG., **60**:144-148. 1943.

A case report.—W. A. B.

Leiomyoma of the Colon. Good, C. A. [*Mayo Clinic, Rochester, Minn.*] RADIOLOGY, **39**:731-732. 1942.

A case is reported of leiomyoma of the transverse colon in a 46 year old man. The only symptoms were recurrent attacks of left upper quadrant pain accompanied by fever, chilliness, and diarrhea. The diagnosis was suspected roentgenologically and confirmed surgically. Two roentgenograms are reproduced.—C. E. D.

Cancer of the Stomach. Gray, H. K. [*Mayo Clinic, Rochester, Minn.*] PROC. MAYO CLINIC, **16**:65-66. 1941.

In the light of present knowledge only the surgeon can offer a patient afflicted with cancer of the stomach the possibility of permanent relief, for early removal of the malignant growth is the only known method of cure. Unfortunately there persists among the public and many members of the medical profession a disregard of the significance of persistent symptoms referable to the stomach. There is an equally deplorable tendency on the part of physicians to await the development of a clinical history typical of that ascribed in textbooks to malignant gastric lesions, before serious consideration is given to the possibility that a malignant lesion of the stomach exists.—J. L. M.

Chronic Gastritis. Its Relation to Gastric and Duodenal Ulcer and to Gastric Carcinoma. Hebbel, R. [*Univ. of Minnesota, Minneapolis, Minn.*] AM. J. PATH., **19**:43-71. 1943.

A study was made of 260 stomachs obtained at autopsy, 106 stomachs resected for duodenal or gastric ulcer, and 52 stomachs resected for carcinoma. There was no evidence that the carcinomas arose with unusual frequency in stomachs already the seat of a diffuse gastritis.—J. G. K.

Cancer of the Stomach: With Special Reference to Early Diagnosis. Held, I. W., and Busch, I. [*New York, N. Y.*] ANN. INT. MED., **18**:719-735. 1943.

A clinical discussion with 6 illustrative roentgenograms.—J. G. K.

Benign Tumors of the Large Intestine—Incidence and Distribution. Helwig, E. B. [*Washington Univ. Sch. of Med., St. Louis, Mo.*] SURG., GYNEC. & OBST., **76**:419-426. 1943.

Polyps were encountered in the large intestine in 154 cases in a study of 1,460 consecutive autopsies. There were 139 cases with adenomas. The latter were usually multiple and occurred most frequently in the sigmoid colon, 13 with lipomas, 1 with a rectal carcinoid tumor, and 1 with a leiomyoma. All carcinomas and sarcomas were excluded from the study, though a few of the adenomas manifested microscopic foci of carcinomatosis. Thirteen figures illustrate the types of lesions.—J. G. K.

Carcinoma of the Stomach. Hibbard, J. S. [*Wichita, Kans.*] J. KANSAS M. SOC., **43**:256-258. 1942.

A review.—C. W.

The Relationship of Polyps of the Colon to Carcinoma. Jackman, R. J. [*Mayo Clinic, Rochester, Minn.*] PROC. MAYO CLINIC, **16**:11-12. 1941.

Some carcinomas of the colon probably begin as polypoid lesions of the mucosa. For this reason the early growth should be destroyed. A case is reported.—J. L. M.

Relation of Atrophic Gastric Mucosa to Carcinoma of the Stomach. Jankelson, I. R., McClure, C. W., and Freedberg, H. [*Boston City Hosp., Boston, Mass.*] REV. GASTROENTEROL., **10**:26-31. 1943.

Atrophy of the gastric mucosa, with or without pernicious anemia, should be considered a precancerous lesion, since in the authors' experience about 4% of such lesions become malignant. This development of gastric cancer is probably associated with the presence of polyps and is almost invariably preceded by a condition in which achlorhydria is present even after administration of histamine.—H. G. W.

Perforated Leiomyoma of Meckel's Diverticulum. Report of a Case. Koucky, J. D., and Beck, W. C. [*Univ. of Illinois, Chicago, Ill.*] SURGERY, **10**:636-641. 1941.

A report of a case.—W. A. B.

The Bad Record of Cancer of the Stomach. Lahey, F. H. [*Lahey Clinic, Boston, Mass.*] LAHEY CLINIC BULL., **3**:2-5. 1942.

Early diagnosis of cancer of the stomach is difficult since hemorrhage, obstruction, severe digestive disturbance, and low gastric acidity may not appear until after metastasis has occurred. A gastric carcinoma palpable through the abdominal wall can rarely be cured. Distaste for food has been noted at the Lahey Clinic as one of the early suggestive symptoms, and, if associated with low values in gastric acidity, loss of weight, vague digestive disturbances, or constipation, it warrants careful study of the patient. If the x-ray studies are inconclusive or reveal a poorly defined abnormality, they must be checked at frequent intervals.

Distant metastases contraindicate operation. If the abdomen is explored, resection should not be begun until careful palpation has shown that the regional extensions will permit complete removal of the tumor. On the basis of extensive experience with subtotal gastrectomies, 55 total gastrectomies, and 7 transpleural resections of the esophagus or cardia for malignancy, it is suggested: (1) that it is desirable to remove the omentum together with the stomach in subtotal gastrectomy; (2) that total gastrectomy can be done in cases of linitis plastica with an operative mortality of not over 15%; (3) that total gastrectomy is often simplified by splenectomy; and (4) that transpleural resection is often warranted and can be done with reasonable safety in carcinoma of the lower esophagus and cardiac end of the stomach.—C. E. D.

One-Stage Radical Resection of the Rectum by Modified Lloyd-Davies Technic. Laufman, H., and Bettman, R. B. [*Michael Reese Hosp., Chicago, Ill.*] AM. J. SURG., **60**:243-247. 1943.

Abdominoperineal resection is carried out with the patient in a combined lithotomy and Trendelenburg position. The abdominal and perineal parts of the operation can proceed simultaneously with shortening of the operative time.—W. A. B.

Two-Stage Resection of Carcinoma of the Ampulla of Vater. Moreland, R. B., and Freeman, B. S. [*Hines Memorial Hosp., Hines, Ill.*] SURGERY, **9**:712-719. 1941.

Successful resection followed by death 5 months later. At autopsy there were metastases in the liver, suppurative cholangitis, and hepatatis.—W. A. B.

Hemangioma of the Stomach. Review of the Literature and Report of Two Cases. Morton, C. B., and Burger, R. E. [*Univ. of Virginia Sch. of Med., University, Va.*] SURGERY, **10**:891-898. 1941.

A report of 2 cases.—W. A. B.

Multiple Gastric Polyposis. A Supplementary Report of 41 Cases, Including 3 New Personal Cases. Pearl, F. L., and Brunn, H. [*Mt. Zion Hosp., San Francisco, Calif.*] SURG., GYNEC. & OBST., **76**:257-281. 1943.

A review of 38 reports found in the literature, to which 3 personal cases are added, shows that in 19 cases malignant alterations were found. The large proportion of patients with malignant change argues for radical resection as the treatment of choice.—H. G. W.

Excision of the Duodenum and Head of the Pancreas for Carcinoma of the Ampulla. Method of Anastomosing Pancreatic Duct to the Jejunum. Phillips, J. R. [*Houston, Tex.*] AM. J. SURG., **60**:137-139. 1943.

A case report.—W. A. B.

Metastatic Melanotic Sarcoma to the Ileum Causing Intussusception. Phillips, J. R. [*Houston, Tex.*] AM. J. DIGEST. DIS., **10**:147-148. 1943.

A report of a secondary tumor in the ileum giving signs of intestinal obstruction and tarry stools. Diagnosis was established by necropsy.—E. E. S.

Carcinoma of the Colon and Rectum. 228 Cases from the Charity Hospital of Louisiana at New Orleans from 1935 to 1941. Romano, S. A., and Trachtenberg, W. [*Louisiana State Univ. Sch. of Med., New Orleans, La.*] NEW ORLEANS M. & S. J., **95**:455. 1943.

A review of 228 records of patients with a diagnosis of carcinoma of the large bowel studied at New Orleans Charity Hospital from 1935 to 1941. The operability increased from 24 to 70% in 7 years, and the operative mortality decreased from 71 to 28%. The highest incidence was in the higher age groups, but 17% of the patients were under the age of 40. More than half the lesions were situated in the rectum. The symptoms and physical findings are discussed. Emphasis is laid on the need for preliminary exploration and decompression when obstruction exists. A program of preoperative and postoperative care is outlined.—E.E.S.

Complex Tridermal Teratoma of the Stomach (Benign). Case Report. Selman, A. N. [*Nyack Hosp., Nyack, N. Y.*] AM. J. SURG., **59**:567-570. 1943.

Report of a tumor measuring $15 \times 10 \times 8$ cm. removed by operation from a 3 months old child.—H. G. W.

Tumors of the Rectum. Smiley, K. E. [*Los Angeles, Calif.*] CALIFORNIA & WEST. MED., **57**:310-313. 1942.

Discussion of polyploid lesions of the rectum.—W. A. B.

Cancer of the Stomach. Snyder, H. E. [*Winfield, Kans.*] J. KANSAS M. SOC., **43**:58-60. 1942.

A review for the layman.—C. W.

Primary Carcinoma of the Stomach with Metastases to Skin and Subcutaneous Tissue. A Case Report. Stein, J. J. [*Veterans' Administration Facility, Hines, Ill.*] U. S. NAV. M. BULL., **40**:708-710. 1942.

A case report and review of the literature.—C. W.

Carcinoid Tumors of the Rectum Derived from Erspamer's Pre-Enterochrome Cells. Stout, A. P. [*Coll. of Physicians and Surgeons, New York, N. Y.*] AM. J. PATH., **18**:993-1009. 1942.

Six probable carcinoid tumors of the rectum are described. Five of them differ cytologically from the common carcinoids found in the appendix and ileum. It is suggested that these are carcinoid tumors composed of Erspamer's pre-enterochrome cells.—J. G. K.

Some Problems in the Diagnosis of Cancer of the Colon and Rectum. Trasoff, A., and Goodman, D. H.

[*Mt. Sinai Hosp., Philadelphia, Pa.*] Am. J. Digest. Dis., **10**: 132-133. 1943.

One hundred and twenty records of patients with proved carcinoma of the colon and rectum were reviewed. Sixty-eight patients were males. Of the tumors, 40% occurred in persons from 50 to 60 years of age. Abdominal pain was the most common early symptom. Constipation was common when the tumor involved the left side of the colon. Anemia was present in the majority of cases. A mass was felt more often when the carcinoma arose from the rectum.—E. E. S.

Cancer of the Rectum. Womack, N. A. [*Washington Univ. Sch. of Med., St. Louis, Mo.*] J. Kansas M. Soc., **42**: 369-374. 1941.

A review with an interesting account of the first colostomy operation in 1776.—C. W.

Primary Carcinoma of the Appendix Associated with Acute Appendicitis. Report of a Case. Young, E. L., and Wyman, S. [*Faulkner Hosp., Boston, Mass.*] New England J. Med., **227**:703-705. 1942.

A case report with a review of the literature for the past 10 years. True carcinoma confined to the apex is found to be quite rare.—C. W.

Liver

Carcinoma of the Larger Bile Ducts. White, R. J. [*Fort Worth, Tex.*] Texas State J. Med., **38**:645-649. 1943.

Four cases with fatal termination are recorded. All had obvious clinical evidence of severe obstructive jaundice, but accurate preoperative diagnosis was not possible. In 2 patients, laparotomy disclosed inoperable masses at the junction of the cystic and hepatic ducts, while in 2 others small tumors were present in the region of the ampulla of Vater. Attempts at radical resection in the latter cases did not appear advisable.—M. J. E.

Bone and Bone Marrow

Malignant Degeneration in a Case of Multiple Benign Exostoses. With a Brief Review of the Literature. Bennett, G. E., and Berkheimer, G. A. [*Johns Hopkins Hosp., Baltimore, Md.*] Surgery, **10**:781-792. 1941.

A case report.—W. A. B.

Stilboestrol and Deep X Rays for Sarcomatous Metastases. Binnie, G. G. [*North Staffordshire Royal Infirmary, Stoke-on-Trent, England*] Brit. M. J., **2**:766-767. 1942.

A case is recorded in which a large metastatic deposit from an osteogenic sarcoma almost entirely disappeared following a course of deep x-ray therapy combined with the injection of stilbestrol in comparatively large doses. The patient, a female aged 18, had an osteosarcoma (spindle cell, with pleomorphism) at the upper end of the tibia, showing irregular absorption and sclerosis of bone. An intensive course of deep x-ray therapy was given, but no response occurred apart from relief of pain, and radiographs showed that bone destruction was continuing. Eight months later a mass 6 cm. in diameter was present in the groin. As in the case of the primary growth, no response occurred after deep x-ray treatment, and the tumor soon began to ulcerate. Deep x-ray treatment was repeated, on this occasion combined with the administration of stilbestrol. The result proved striking, and the fungating tumor gradually disappeared, leaving a clean cavity with small amounts of tumor tissue still present in the walls. The ulcer, which was at one time 8.5 cm. in diameter, decreased to 3.5×5.0 cm. Another extraordinary feature was the sharp definition of a metastatic deposit in the lungs. The initial dose of stilbestrol was 5 mgm. intramuscularly daily for 1 week, increased to 7.5 mgm. daily for 12 days. After an interval of 2 weeks, 10 mgm. was given intramuscularly daily for 22 doses.

Another case is mentioned (of osteochondrosarcoma of the femur with recurrence in the stump) that was similarly treated. The result was not so definite, although some retardation of the rate of growth took place.—A. H.

Bone Tumors with Reference to Their Treatment. Copeland, M. M. [*Johns Hopkins Med. Sch., Baltimore, Md.*] Surgery, **11**:436-455. 1942.

A general review.—W. A. B.

Aberrant Thyroid Tumor of the Vertebrae with Compression of the Spinal Cord. Denker, P. G., and Osborne, R. L. [*Bellevue Hosp., New York, N. Y.*] Arch. Neurol. & Psychiat., **49**:227-281. 1943.

The paper reports the case of a vertebral tumor, composed of normal thyroid tissue, with secondary compression of the cord. The treatment consisted of surgical removal of the tumor, which had to be repeated, and high voltage irradiation. The patient appears to be cured 8 years after the last operation.—A. C.

Cavernous Hemangioma of the Skull. Case Report. Echols, D. H., and Kleinsasser, L. R. J. [*Tulane Univ. Sch. of Med., New Orleans, La.*] Am. J. Surg., **60**:134-136. 1943.

A case report.—W. A. B.

Cystic Myxomatous Tumors about the Knee: Their Relation to Cysts of the Menisci. Ghormley, R. K., and Dockerty, M. B. [*Mayo Clinic, Rochester, Minn.*] J. Bone & Joint Surg., **25**:306-318. 1943.

Four cases with mucinous tumors of the knee joint are described. The tumors are thought to result from cystic degeneration followed by extensive repair and are not regarded as examples of true neoplasms.—E. E. S.

Osteoid-Osteoma of the Astragalus. Horwitz, T. [*Philadelphia, Pa.*] Radiology, **39**:226-228. 1942.

A benign tumor of bone, typical of "osteoid-osteoma" as described by Jaffe, was found in the astragalus of a 16 year old Negro boy. Radiologically the lesion appeared as an oval, sharply defined, radiolucent nodule elevating the overlying intact cortical bone like a blister. There was an increase in density of the surrounding bone but no soft tissue reaction. The tumor was excised. Two photomicrographs are reproduced, which show a vascular tumor with abundant osteoid formation and many giant cells. Such lesions may be misdiagnosed as sclerosing nonsuppurative osteomyelitis of Garré or as intracortical bone abscess.—C. E. D.

Benign Chondroblastoma of Bone. A Reinterpretation of the So-Called Calcifying or Chondromatous Giant Cell Tumor. Jaffe, H. L., and Lichtenstein, L. [*Hosp. for Joint Diseases, New York, N. Y.*] Am. J. Path., **18**:969-991. 1942.

The authors describe as benign chondroblastoma of bone a lesion that has previously been considered a

variety of giant cell tumor. The growth starts its development in an epiphysis, usually of some long bone, not necessarily the humerus; it rarely attains a size of more than 3 to 5 cm. in largest diameter. The lesion occurs particularly in males, almost always in adolescents. It proves benign and heals without recurrence after curettage.

The basic tumor cells of the lesion are polyhedral or round and of moderate size, with a fairly large nucleus, and are held by the authors to be chondroblasts. The tumor cells may be closely packed or more loosely agglomerated, but the distinctive feature is the presence of focal areas of calcification of the cellular tumor tissue. Wherever the calcification becomes intense the tumor cells swell and undergo necrosis. The necrotic tumor tissue comes to be replaced by hyaline chondroid tissue, which subsequently may show spots of ossification. There may be areas of hemorrhage and also large vascular sinuses bordered by viable tumor tissue, necrotic tumor tissue, or hyaline chondroid material that has replaced the necrotic tumor tissue. Clumps of large multinuclear giant cells may be seen in the areas of hemorrhage, about the vascular sinuses, and even in the hyaline chondroid tissue; these the authors regard as multinuclear macrophages such as are commonly found in skeletal lesions in the vicinity of local hemorrhage, organization, fibrosis, chondrification, or ossification. Occasionally, a few small giant cells (with 2 or 3 or even several more nuclei), which may be actual tumor giant cells formed by the fusion of smaller unicellular cells, are distributed amongst the polyhedral tumor cells.

Excellent figures illustrate the lesion in its major aspects. The authors discuss why they regard its basic tumor cells as cartilage germ cells, and how the lesion differs from the giant cell tumor of bone on the one hand and from the ordinary benign chondroma on the other.—J. G. K.

Osteochondromas Arising from the Base of the Skull. List, C. F. [*Univ. of Michigan, Ann Arbor, Mich., and Yale Univ. Sch. of Med., New Haven, Conn.*] Surg., Gynec. & Obst., **76**:480-492. 1943.

Seven cases are reported. In 5 the lesion originated extradurally from the sphenoid bone, protruding intracranially in 4; in the other 2 cases the neoplasm originated extracranially in the ethmoidal region, invaded paranasal sinuses, and finally extended into the cranial cavity. The histological, clinical, and surgical aspects of the lesion are discussed.—J. G. K.

Metastatic Lesions of the Sternum. Macey, H. B., and Phalen, G. S. [*Mayo Clinic, Rochester, Minn.*] Surg., Gynec. & Obst., **76**:453-455. 1943.

Two cases are reported of metastatic lesions involving the sternum, possibly from primary pulmonary adenocarcinomas.—J. G. K.

Sacrococcygeal Chordoma. Report of a Case. Olsman, L., and Lev, M. [*Chicago State Hosp., Chicago, Ill.*] Am. J. Surg., **60**:115-118. 1943.

A case report.—W. A. B.

Ewing's Tumor. Report of a Case Demonstrating the Characteristic Periodic Course. Roberts, C. P. [*Tufts Coll. Med. Sch., Boston, Mass.*] New England J. Med., **226**:90-97. 1942.

A case report and review of mortality statistics.—C. W.

"Silent" Skeletal Metastases in Cancer. Stein, R. J. [*Orleans County Mem. Hosp., Newport, Vt.*] Am. J. Clin. Path., **13**:34-41. 1943.

A search was made at necropsy for microscopic bone metastases in 78 cases of cancer of various types. These were found: in 60% of 23 cases of carcinoma of the breast, in 68% of 16 cases of prostatic cancer, in 25% of 20 cases of cancer of the cervix, and in 1 of 6 cases of carcinoma of the stomach. The metastatic nodules were almost always multiple; they were invariably present in red marrow and not in yellow; frequently they had not elicited symptoms during life. Eight figures illustrate the article.—J. G. K.

Metastatic Malignancy of the Spine. Toumey, J. W. [*Lahey Clinic, Boston, Mass.*] J. Bone & Joint Surg., **25**:292-305. 1943.

The records of 95 patients having roentgenographic evidence of tumor metastases of various types in the spine were reviewed. The majority of tumors were derived from the breast or prostate. Roentgenotherapy afforded the greatest relief of pain. The efficacy of cobra venom, subarachnoid alcohol injection, chordotomy, application of braces, and orchiectomy is discussed.—E. E. S.

Leukemia, Lymphosarcoma, Hodgkin's Disease

Leukemia: The Relative Incidence of Its Various Forms, and Their Response to Radiation Therapy. Bethell, F. H. [*Univ. of Michigan, Ann Arbor, Mich.*] Ann. Int. Med., **18**:757-771. 1943.

Four hundred and ninety-five cases, seen during 14½ years, are classified as lymphogenous (43.6%), myelogenous (48.3%), and histogenous (undifferentiated or slightly differentiated reticulum cells, 8.1%). The sex and median age of the patients and the frequency of cases of the several types are tabulated; an apparent increase in the incidence of the disease is noted. Hematologic data on 4 illustrative cases are reported. Roentgen therapy of leukemia is discussed, and the results of such treatment are presented.—J. G. K.

A Study of Lymphosarcoma and Leukemias, Including Two Chloromas. Griffin, L. L., and Brindley, P. [*Univ. of Texas, Galveston, Tex.*] Texas State J. Med., **38**:22-27. 1942.

The authors tabulate the incidence of leukemic and allied diseases occurring in a group of necropsies done at the University of Texas between 1892 and the present time. Among 5,400 postmortem examinations, 9 examples of lymphosarcoma or chronic lymphatic leukemia were observed; 8 of chronic myeloid leukemia; 8 of acute leukemia; 1 each of leukosarcoma and Hodgkin's disease, the latter associated with a blood picture suggesting eosinophilic leukemia; and 2 of chloroma. The latter are discussed in some detail.—M. J. E.

Panel Discussion on the Leukemias and Lymphoblastomas. Newell, R. R., Falconer, E. H., Hill, H. P., Lawrence, J. H., Wood, D. A., and Wyckoff, H. [*Stanford*

Univ. Hosps., San Francisco, Calif.] RADIOLOGY, **39**:298-305. 1942.

Many aspects of the classification, treatment, and prognosis of leukemia and lymphoblastoma are discussed informally. The available classifications are unsatisfactory since they are morphological rather than etiological. Radiation is the most useful agent in the palliative therapy of chronic leukemia, but some cases will still respond to arsenic after they have become refractory to radiation. Patients with acute leukemia are seldom or never benefited by radiation. Therapy should be directed toward improving the patient's clinical condition, rather than toward reducing the white blood cell count to normal. Anemia and leukopenia may result from radiation or arsenic therapy and sometimes necessitate transfusions.

In Hodgkin's disease, as in leukemia, it is desirable to use the smallest dose of roentgen rays that will relieve the patient's symptoms. Radioactive phosphorus is effective in leukemia but not in Hodgkin's disease.

In certain cases lymphosarcoma may be a localized disease in its early stages and hence curable by surgery or heavy irradiation. Unfortunately in most cases the disease is generalized when first seen and is best treated symptomatically.—C. E. D.

Chronic Leukemia: a Statistical Study of Symptoms, Duration of Life, and Prognosis. Pascucci, L. M. [*Coll. of Physicians and Surgeons, New York, N. Y.*] RADIOLOGY, **39**:75-80. 1942.

A statistical study is presented of the relation of signs and symptoms to life expectancy in 64 cases of myeloid leukemia and 64 cases of lymphatic leukemia seen at the Presbyterian Hospital between 1919 and 1939. All patients received roentgen therapy. The average age of onset was 41.1 and 49.6 years for myeloid and lymphatic leukemia respectively. The 64 myeloid cases were equally divided between men and women, while 58% of the lymphatic group were men. Initial symptoms of weakness and loss of weight, and symptoms attributable to splenic enlargement, were more common in the myelogenous group. Enlargement of superficial lymph nodes was the initial complaint in 63% of the lymphatic group and 20% of the myelogenous group. The average survival was 2.5 and 2.8 years among patients with myeloid and lymphatic leukemia respectively. The corresponding 5 year survivals were 5% and 14.5%. Tables and charts are presented to show, among other things, that early anemia and thrombocytopenia are bad prognostic signs. Radiation therapy affords symptomatic relief but has not been definitely shown to prolong life.—C. E. D.

SPLEEN

Calcified Cystic Tumor of the Spleen. Culver, G. J., Becker, C., and Koenig, E. C. [*Buffalo Gen. Hosp., Buffalo, N. Y.*] RADIOLOGY, **39**:62-68. 1942.

A case is reported of partially calcified cystic angioma of the spleen in a 25 year old white woman. The tumor was diagnosed roentgenologically as a splenic cyst and was successfully removed. Roentgenograms and photographs of gross specimens and of sections are presented.—C. E. D.

ADRENAL

Vaginal Metastasis from Hypernephroma. Kurzrok, L., and Fenichel, N. [*Jewish Hosp., Brooklyn, N. Y.*] AM. J. SURG., **58**:142-144. 1942.

A case report.—H. G. W.

Malignant Pheochromocytoma of the Adrenal Medulla (Paraganglioma). Report of a Case Simulating Carcinoma of the Adrenal Cortex with Secondary Adrenal Insufficiency. McGavack, T. H., Benjamin, J. W., Speer, F. D., and Klotz, S. [*New York Med. Coll. and Metropolitan and Flower-Fifth Avenue Hosps., New York, N. Y.*] J. CLIN. ENDOCRINOL., **2**:332-338. 1942.

A case report with findings at autopsy of a 43 year old woman with malignant paraganglioma of the adrenal medulla. This is the eighth recorded case. Differences in the clinical course of benign and malignant forms of pheochromocytoma of the adrenal glands are discussed, with emphasis placed upon the absence of bouts of paroxysmal hypertension in the malignant forms. An unusual feature in this instance is the Addisonian-like syndrome in the presence of a histologically normal pituitary gland and adrenal cortex.—J. B. H.

Adrenal Tumor in Female Infant. With Hypertrichosis, Hypertension, Overdevelopment of External Genitalia, Obesity, but Absence of Breast Enlargement. Neff, F. C., Tice, G., Walker, G. A., and Ockerblad, N. [*Sch. of Med., Univ. of Kansas, Kansas City, Kans.*] J. CLIN. ENDOCRINOL., **2**:125-127. 1942.

This is a case report covering the preoperative and postoperative history of a female infant with an adrenal medullary tumor, hypertension, obesity, and development of some secondary sexual characteristics. When the child was 8 months of age, a heavy growth of hair was observed over the body. This was followed by the appearance of acne, obesity, hypertrophy of the labiae, a systolic blood pressure of 140 to 200 mm. of mercury, a count of 6,830,000 red cells, and advancement in osseous age. At operation, when the infant was 17 months old, a 96 gm. tumor was removed from above the left kidney and diagnosed as chromaffinoma or pheochromocytoma. The adrenal cortical tissue appeared to be normal. Within 6 months after operation the excessive growth of hair, the acne, and the obesity were noticeably diminished.—J. B. H.

Adrenal Cortex Carcinoma. Rettenmaier, A. J., Allen, M. S., and Liddy, E. D. [*Kansas City and Lawrence, Kans.*] J. KANSAS M. SOC., **42**:471-474. 1941.

A case report and review of the literature.—C. W.

Diabetes Mellitus without Other Endocrine Manifestations in a Case of Tumor of the Adrenal Cortex. Sprague, R. G., Priestley, J. T., and Dockerty, M. B. [*Mayo Clinic, Rochester, Minn.*] J. CLIN. ENDOCRINOL., **3**:28-32. 1943.

This is stated to be the only recorded case in which diabetes mellitus was the sole endocrine disturbance associated with a tumor of the adrenal cortex. The patient was a 49 year old woman with glycosuria, which was not entirely controlled by large doses of insulin. Values for blood sugar were higher than normal. With removal of a large semi-encapsulated yellow tumor from the right adrenal gland, the carbohydrate metabolism became nor-

mal as determined by glucose tolerance tests. The tumor was described as an adenocarcinoma of the adrenal cortex.—J. B. H.

Pancreas

Functioning Islet Cell Carcinoma with Metastases to Liver. Gray, L. M. [*New England Deaconess Hosp., Boston, Mass.*] Am. J. Path., **18**:633-643. 1942.

A case is reported of islet cell carcinoma of the pancreas with symptoms and signs of severe hypoglycemia. Beta cells were demonstrated in the primary tumor but not in the metastatic lesions. Pituitary basophilism also was found. A comparison is made with 8 other cases of proved islet cell carcinoma with metastases. Six illustrations.—J. G. K.

Metastatic Carcinoma of Skeletal Muscles. Mulsow, F. W. [*Cedar Rapids, Iowa*] Arch. Path., **35**:112-114. 1943.

A case of carcinoma of the pancreas with metastases to many of the skeletal muscles is reported.—H. G. W.

Carcinoma of Tail of Pancreas with Small Bowel Perforation and Peritonitis. Congenital Anomalies of Esophagus and Subclavian Artery. Tollman, J. P., and Kreig, J. [*Univ. of Nebraska Coll. of Med., Omaha, Neb.*] Nebraska State M. J., **26**:286-287. 1941.

In a case of carcinoma of the tail of the pancreas, the patient died of peritonitis following invasion and perforation of the ileum. The congenital anomalies referred to in the title were unrelated to the tumor.—M. J. E.

Pituitary

Treatment of Gigantism: Observations on a Pituitary Giant for Six Years. Hurxthal, L. M. [*Lahey Clinic, Boston, Mass.*] J. Clin. Endocrinol., **3**:12-19. 1943.

This is a description of changes observed in a giant between his fifteenth and twenty-second years, and of attempts to suppress his excessive growth. Serial studies were made roentgenographically of the epiphyses and sella turcica, and detailed records kept of the body weight and appearance of the external genitalia. Therapeutic trials included irradiation of the pituitary gland and administration of gonadotropins and testosterone compounds.—J. B. H.

Thyroid

The Parathyroid Glands. Malignant Tumor with Osteitis Fibrosa Cystica. Gentile, R. J., Skinner, H. L., and Ashburn, L. L. [*U. S. Marine Hosp., Baltimore, Md.*] Surgery, **10**:793-810. 1941.

A case report with a review of 21 cases of malignant parathyroid tumors described in the literature.—W. A. B.

Multiple Tumors

Metachronous Multiple Malignancies in 5,876 Cancer Patients. Peller, S. [*Johns Hopkins Univ., Baltimore, Md., and New York Univ., New York, N. Y.*] Am. J. Hyg., **34-A**:1-11. 1941.

Study of the frequency of new primary cancers occurring some time after another earlier cancer has been cured may reveal whether or not the general resistance to new growths is greater in persons who, at some time previously, were susceptible. The method used in the present work was to examine the records of cancer patients in order to discover whether an earlier cancer had been cured before the current cancer disease had apparently started. Only the combinations surface-internal malignancy, internal-surface cancer, and internal-internal tumors were considered. Records of 5,876 patients, all over 50 years of age, were studied, no incomplete history being rejected if the existence of another primary cancer in the past could be established with some probability. The number of metachronous malignant tumors actually found was compared with the expected number, the calculations being based on survival rates. The results indicate that metachronous primary malignant tumors are several times less frequent than would be expected if the development of one tumor in a susceptible person is assumed to be independent of the existence of another primary tumor in the past. It appears, therefore, that a cured tumor in the history of a patient coincides with a state of resistance of the body against the development of other malignant neoplasms. This remnant protection, though not unfailing, seems to be strong enough to justify an attempt to change the distribution of cancer by site.—A. C.

Incidence of Multiple Primary Tumors and the Problem of Acquired Cancer Immunity. Schmidt, E. A. [*Univ. of Colorado Sch. of Med. and Hosps., Denver, Colo.*] Radiology, **39**:208-213. 1942.

Among 3,700 consecutive autopsies at the University of Colorado Medical School, 42 examples of multiple primary benign or malignant tumors were found. In only 10 instances, or 0.27% of the total autopsies, were two or more malignant tumors present. The opinion of Peller that a skin tumor confers protection against internal tumors is cited, and some of the work on tumor immunity in experimental animals is discussed. It is suggested that the rarity of multiple human tumors may well be due to some process of acquired immunity, which could, in the future, play an important part in tumor prophylaxis or therapy. No calculation is presented of the expected incidence of multiple tumors in the author's series of autopsies.—C. E. D.

Association of Renal and Vesical Neoplasms: Report of Two Cases. Schulte, T. L., and Priestley, J. T. [*Mayo Clinic, Rochester, Minn.*] Proc. Staff Meet., Mayo Clin., **16**:381-383. 1941.

Two cases of coexistent vesical and renal neoplasm are reported because of several unusual features. In the first case, vesical, renal, and ureteral lesions were present and were all of the same type and grade; in the second case, the patient had an adenocarcinoma of the kidney and an epithelioma of the bladder, an unusual occurrence.—J. L. M.

Multiple Primary Malignant Lesions. Two Case Reports. Wehrbein, H. L., and Weber, J. J. [*Lutheran Hosp., Brooklyn, N. Y.*] Am. J. Surg., **61**:143-147. 1943.

Two case reports: one, carcinoma of the stomach with metastases to the liver and carcinoma of the prostate with metastases to bones; the other, carcinoma of the prostate and rhabdomyosarcoma of the bladder.—W. A. B.

MISCELLANEOUS

Kaposi's Sarcoma. A Critical Survey. Aegerter, E. E., and Peale, A. R. [*Temple. Univ. Sch. of Med., Philadelphia, Pa.*] ARCH. PATH., **34**:413-422. 1942.

A critical review leads to the conclusion that the neoplasm in question is the cancerous representative of the tumors of the blood vessels and that as such it should be called "angiosarcoma," the term "Kaposi's sarcoma" being reserved for the subvariety that arises in the skin. Four cases are presented, in one of which the tumor was limited to the heart.—H. G. W.

Clinico Pathological Conference. Barden, R. P., Belk, W. P., Pratt, G. E., and Taylor, W. R. [*Hosp. of Protestant Episcopal Church, Philadelphia, Pa.*] RADIOLOGY, **39**:334-336. 1942.

The subject of this conference was a 5 year old white boy with a leukopenic anemia, relative lymphocytosis, and widespread rarefying lesions of bone. The clinician made a diagnosis of leukemia, the radiologist, of sympathetic neuroblastoma with skeletal metastases, and the pathologist, of Ewing's endothelial myeloma with extensive skeletal involvement.—C. E. D.

Cancer in the Male: Discovered in a Clinic Treating Genito-Infectious Diseases. Brunet, W. M. [*Pub. Health Inst., Chicago, Ill.*] VIRGINIA M. MONTHLY, **68**: 693-696. 1941.

Cancer was discovered in 75 patients while they were under treatment for genitourinary infections. A discussion of the role played by syphilis in malignancy, especially of the mouth, tongue, and throat, is given.—M. E. H.

Lipoma of the Thigh: Report of a Case. Coventry, M. B., and Ghormley, R. K. [*Mayo Clinic, Rochester, Minn.*] PROC. STAFF MEET., MAYO CLIN., **16**:697-699. 1941.

Diagnosis of tumors of the upper and inner aspect of the thigh is not easy, and great harm can be done by cutting into certain nonneoplastic masses, such as aneurysms, hernias, or psoas abscesses. To emphasize this point, as well as to show that the diagnosis of lipoma usually can be made before operation, the authors report a case.—J. L. M.

"Cylindroma" (Adenocarcinoma, Cylindroma Type). Report of Two Cases with Metastases. Dockerty, M. B., and Mayo, C. W. [*Mayo Clinic, Rochester, Minn.*] SURGERY, **13**:416-422. 1943.

A report of 2 cases with metastases. One arose in the tongue, the other probably in the parotid gland.—W. A. B.

Sex Hormones and Their Effects on Certain Cancerous and Noncancerous Conditions. Essenberg, J. M., Blum, V. G., Schmitz, H. E., and Orndorff, B. H. [*Chicago, Ill.*] PROC. INST. MED. CHICAGO, **14**:372-374. 1943.

The regular meeting of the Chicago Roentgen Society for January 14, 1943, was a symposium at which the anatomy and embryology of the reproductive systems were reviewed and the developmental history of the suprarenal cortex was considered. The effects of male and female gonadal hormones on the prostate gland were outlined. In the management of neoplasms whose growth is influenced by sex hormones, the quick withdrawal of the latter is one of the most important advances in clinical medicine. This may be accomplished by surgery, endocrinotherapy that neutralizes a primary hormone, or radiotherapy.—M. E. H.

Mesotheliomas of the Uterine and Tubal Serosa and the Tunica Vaginalis Testis. Report of Four Cases. Evans, N. [*Coll. of Med. Evangelists, Los Angeles, Calif.*] AM. J. PATH., **19**:461-471. 1943.

Four tumors of similar histological structure are described that seemed to originate from the serous membranes of male and female generative organs. The tumors were classified as mesotheliomas and appeared to be benign. Similar growths have been described previously but have been variously classified, usually as adenomas or adenocarcinomas. There are 7 figures.—J. G. K.

Tumor of the Carotid Body and the Pancreas. Goodof, I. I., and Lischer, C. E. [*Washington Univ. Sch. of Med. and Barnes Hosp., St. Louis, Mo.*] ARCH. PATH., **35**: 906-911. 1943.

Histologically identical tumors ("chromaffinomas") were present in the carotid body and pancreas of a 47 year old Negro. The question of metastasis or multicentric origin is discussed.—J. G. K.

Tumors of the Carotid Body. Clinical and Pathologic Considerations of Twenty Tumors Affecting Nineteen Patients (One Bilateral). Harrington, S. W., Clagett, O. T., and Dockerty, M. B. [*Mayo Clinic, Rochester, Minn.*] ANN. SURG., **114**:820-833. 1941.

Tumors of the carotid body, although relatively rare, should always be considered in the differential diagnosis of tumors of the upper anterior neck regions. They are always malignant or potentially malignant tumors.

Treatment should be complete surgical removal. Ligation of the carotid vessels is necessary in about 50% of the cases, and the complication of ascending thrombosis with hemiplegia is frequent.—M. R. D.

Cystadenoma Lymphomatosum. Henderson, R. C. [*Veterans' Administration, Bronx, N. Y.*] M. BULL. VET. ADMIN., **18**:434-435. 1941-42.

A case report.—M. E. H.

Papillary Cystadenoma Lymphomatosum. Hines, R. E. [*Veterans' Administration, Wichita, Kans.*] M. BULL. VET. ADMIN., **18**:210. 1941-42.

A case report.—M. E. H.

The Pathologist in the Cancer Clinic and in the Hospital. Hirsch, E. F. [*St. Luke's Hosp. and Univ. of Chicago, Chicago, Ill.*] ILLINOIS M. J., **81**:222-224. 1942.

Plea for closer cooperation between the pathologist and the clinician in the handling of the cancer patient.—M. E. H.

Benign Tumors of the Mesentery. Mills, W. M. [*Topeka, Kans.*] J. KANSAS M. SOC., **43**:92-96. 1942.

A review with 2 case reports.—C. W.

STATISTICS

The Reliability of Certificates of Deaths from Cancer. Dorn, H. F., and Horn, J. I. [*Nat. Inst. of Health, Bethesda, Md.*] AM. J. HYG., **34-A**:12-23. 1941.

In a study of the incidence of cancer, conducted in ten urban areas from 1938 to 1940, data were collected by means of a questionnaire mailed to every physician, hospital, and clinic in the study area and, if necessary, by

personal visits. A copy of the death certificate, filed for each person who died from cancer in the area during the study year, was obtained from the local health department. The present study is limited to an analysis of the consistency of the entries for primary site of cancer and age. Case reports and death certificates involving cancer were obtained for 13,524 persons. The closest agreement (92.6%) was found for cancer of the digestive tract. The least agreement occurred for cancer of the skin (42.6%), brain cancer (46.3%), and bone cancer (51.5%). In about three-fourths of the cases, the age obtained in the survey fell in the same five year age group as that recorded on the death certificate. The agreement in age was greater for males than for females and greater for white than for colored persons.—A. C.

Errors in Clinical Statements of Causes of Death. Pohlen, K., and Emerson, H. [*Kellogg Foundation, Battle Creek, Mich., and Coll. of Physicians and Surgeons, New York, N. Y.*] Am. J. Pub. Health, **32**:251-260. 1942.

The validity of a discussion on the apparent increase in mortality from cancer depends on the accuracy with which certification of cause of death has been established. The paper is the application to deaths from malignant tumors of a study of the statistical expression of error in certification of cause of death based upon clinical findings and opinion as compared with postmortem protocols of the same cases. The diagnoses were classified as topographically and etiologically correct, partly correct, and incorrect. Among 3,462 cases of malignant tumors, two-thirds were found to be correct. The number of diagnoses considered partly correct in one or both ways, but in no way completely incorrect, represented 14% of the total cases. Incorrect diagnosis amounted to 6%. By the arrangement of clinical diagnoses according to anatomical site, an 80% accuracy, or more, was found for malignant tumors of breast, rectum (including rectosigmoid), cervix, pharynx and larynx, and esophagus. There was less than 50% correct diagnosis for malignant growths of the liver, small intestine, brain, and bile duct. The range of correct diagnoses at both admission and death was from 87% for breast cancer to less than 2% for bile duct neoplasm. A study of the primary tumor and of metastases as the cause of death is included.—A. C.

Primary Site of Carcinoma of Liver, Lungs, and Bone. Satterlee, R. C. [*Medical Corps, U. S. Navy.*] U. S. Nav. M. Bull., **40**:133-136. 1942.

A statistical analysis of mortality reports.—C. W.

Cancer Data in Kansas. J. Kansas M. Soc., **43**:430-432. 1942.

A statistical summary.—C. W.

CANCER CONTROL AND PUBLIC HEALTH

Results of Fifteen Years of the Cancer Control Program in Massachusetts. Lombard, H. L., and Macdonald, F. A. [*Massachusetts Dept. of Pub. Health, Boston, Mass.*] New England J. Med., **226**:81-84. 1942.

An analysis of records showing the improvement resulting from the Cancer Control Program, and a discussion of the factors involved.—C. W.

SCIENTIFIC SOCIETIES AND RESEARCH ORGANIZATIONS

Annual Report for the Year 1941 of The South African Institute for Medical Research, Johannesburg.

In the section of this report dealing with cancer, Dr. des Ligneris urges the desirability of detailed histories of patients suffering from cancer, and of other patients for comparison, which might suggest precancerous factors. "Every member of the community should have a detailed clinical history, established from the time of birth until the time of death." Cancer patients can be classified in 3 groups; (1) those with a definite history of a precancerous condition; (2) those in the first 35 years of life "in whom we may suspect a definite inherited or constitutional disturbance;" and (3) the remainder, which of course constitutes the great majority; "the number of patients falling within this category should fall appreciably if the above mentioned method of life-long supervision by medical advisers and investigators were established."

The treatment of mice with liver extracts from Bantu and European cancerous and noncancerous persons (des Ligneris, M. J. A., Am. J. Cancer, **89**:489. 1940) was brought to a provisional conclusion. Amongst the last batch of mice that had been treated with noncancerous Bantu liver extracts, a few more skin epitheliomas appeared, and a case of sarcoma was observed in a mouse that died with lung metastases. Other animals, such as rats, sheep, and rabbits, treated with any of these extracts, did not develop tumors, even after 2 years.—E. L. K.